Advanced Gait Analysis:
Insights into
Human Locomotor Control

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This thesis is dedicated to two inspirational young patients and their families:

PW and JS

and to Sarah, Alex & Finn

Contents

Summary

Human walking is the result of a complex interaction of multiple neuroanatomical systems and the relative importance of these systems depends on the locomotor task being performed. An understanding of these relative roles and the consequences of different CNS lesions on locomotion requires comprehensive profiling of human walking behaviours in health and disease. We assessed humans walking on a treadmill under different locomotor conditions using 3D kinematic gait analysis. We revealed task-specific, age-dependent patterns of foot endpoint control in 121 healthy adults. In older adults, cognitive distraction while walking resulted in degraded endpoint control in the form of decreased mean toe clearance and an increase in the frequency of extremely low toe clearance values. This translated into a markedly increased modelled probability of tripping. Conversely, walking with the lower visual field restricted was associated with increased clearance, but in older adults control was intermittently degraded and tripping risk increased. We also examined arm swing behaviour during the Stroop colour-word naming task in 83 healthy adults. Remarkably, increasing difficulty in this left-lateralised language task resulted in significantly increased arm swing asymmetry, driven by a reduction in the movement on the right. We propose that these observations are due to unilateral inhibition of a corticospinal contribution to arm swing. Men of all ages and older women were strongly affected by this phenomenon but women under 60 appeared to be resistant. The reason for this is unclear but may represent oestrogen-dependent plasticity and redundancy in the prefrontal cortex, where activation underpinning cognitive control during the Stroop task is likely to interfere with gait control. This paradigm was then applied to patients with incomplete spinal cord injury (SCI). Patients with thoracic injuries showed a significantly larger, homogeneous shift in arm swing symmetry towards left-dominant patterns during the Stroop task than those with cervical injuries. Patients with thoracic SCI may have longstanding interruption of the long propriospinal connections between the dominant lumbar central pattern generator for locomotion and its subsidiary, cervical component which usually contributes to arm swing. As a result, their arm swing is more dependent on supraspinal control and is susceptible to interference from the Stroop task. These results taken together support an important role of supraspinal centres in diverse aspects of human walking behaviour, from fine control of toe trajectory to the more automatic, rhythmic swinging of the arms.

Zusammenfassung

Der aufrechte Gang des Menschen ist das Resultat aus einem komplexen Zusammenspiel zahlreicher neuroanatomischer Systeme, deren Interaktion davon abhängt, welche Fortbewegungsaufgabe ausgeführt werden soll. Um dieses Zusammenspiel und die Konsequenzen unterschiedlicher Läsionen des Zentralnervensystems auf die Fortbewegung zu verstehen, muss man sowohl das gesunde als auch das pathologische menschliche Gehverhalten umfassend charakterisieren und beschreiben. Mithilfe der kinematischen dreidimensionalen Ganganalyse untersuchten wir auf einem Laufband das menschliche Gehverhalten unter verschiedenen Fortbewegungsbedingungen. Bei 121 gesunden Erwachsenen deckten wir aufgabenspezifische, altersabhängige Muster bei der motorischen Kontrolle des Fuss-Endpunktes auf. Bei älteren Erwachsenen führte eine kognitive Ablenkung während des Gehens zu einer schlechteren Endpunkt-Kontrolle im Sinne einer geringeren durchschnittlichen Schritthöhe (Minimaldistanz zwischen Zehen und Boden während der Schwungphase) und einer Zunahme der Häufigkeit von extrem niedrigen Werten bei der Schritthöhe. Dies entsprach einer deutlich erhöhten modellierten Stolperwahrscheinlichkeit. Im Gegensatz dazu war das Gehen mit eingeschränktem Gesichtsfeld mit einer erhöhten Schritthöhe verbunden. Ältere Probanden zeigten jedoch intermittierend eine schlechtere Kontrolle der Schritthöhe und ein erhöhtes Risiko zu stolpern. Des Weiteren untersuchten wir bei 83 gesunden Erwachsenen den Armschwung während einer Doppelaufgabe. Dabei mussten die Probanden während des Gehens den Farbe-Wort-Interferenztests nach Stroop ausführen. Bemerkenswert war, dass ein zunehmender Schwierigkeitsgrad dieser links lateralisierten Sprachaufgabe zu einer signifikant grösseren Asymmetrie des Armschwungs führte. Die beobachtete Asymmetrie war vor allem auf die Verringerung der rechtsseitigen Bewegung zurückzuführen. Wir halten es für möglich, dass diese Beobachtungen durch eine einseitige Hemmung kortikospinaler Netzwerke, die in der Kontrolle des Armschwungs involviert sind, bedingt sein könnte. Männer aller Altersgruppen und ältere Frauen waren von diesem Phänomen betroffen, Frauen unter 60 Jahren zeigten dieses Verhalten jedoch nicht. Der Grund hierfür ist unklar. Es könnte sich jedoch um eine östrogenabhängige Plastizität und Redundanz im präfrontalen Kortex handeln: dieses Hirnareal ist sowohl für die kognitive Kontrolle als auch die Gangkontrolle zuständig und stellt dadurch die wahrscheinlichste

Lokalisation der Interferenz während der Doppelaufgabe dar. Dieses Paradigma wurde anschliessend auf Patienten mit einer inkompletten Rückenmarksverletzung angewendet. Patienten mit thorakalen Verletzungen zeigten eine signifikant grössere, homogene Verschiebung der Armschwungsymmetrie während des Stroop-Tests hin zu einem links-dominanten Muster als diejenigen mit zervikalen Verletzungen. Bei Patienten mit thorakaler Rückenmarksverletzung liegt eventuell eine anhaltende Unterbrechung der langen propriospinalen Verbindungen zwischen dem dominierenden lumbalen Bewegungsmustergenerator (Central Pattern Generator) und seiner untergeordneten zervikalen Komponente, die normalerweise an der Kontrolle des Armschwungs beteiligt ist, vor. Daraus ergibt sich, dass der Armschwung abhängiger von der supraspinalen Kontrolle und somit störanfälliger durch den Stroop-Test wird. Zusammen unterstützen diese Ergebnisse die Hypothese, dass supraspinale Zentren eine wichtige Rolle bei verschiedenen Aspekten des menschlichen Gehverhaltens spielen, von der Kontrolle der Trajektorie der Zehen bis zum eher automatischen, rhythmischen Armschwung.

General introduction

The control of locomotion in vertebrates

Devonian aquatic tetrapods evolved legged locomotion around 360 million years ago, a critical development which enabled the subsequent colonisation of land.[1] It remains the dominant means of movement for land-dwelling vertebrates, including all terrestrial mammals, the basic body structure of which features two paired sets of limbs which can produce coordinated, rhythmic movements to effect propulsion. These movements are caused by skeletal muscular contraction elicited at the neuromuscular junction by lower motor neurones, signals which represent the net output of an interplay of multiple specialised units of the central nervous system involved in locomotor behaviour.[2–4]

In the spinal cord of vertebrates from fish to mammalian carnivores, there is strong evidence for central patter generators (CPGs),[5–9] capable of generating sequential, rhythmic motor outputs in the absence of a connection to the brain or, in principle, the peripheral nervous system. The importance of afferent inputs from limb muscle stretch receptors and proprioception in *modulating* CPG activity has, however, been demonstrated in a range of animal lesioning experiments;[10] spinalised cats can adjust their stepping frequency to match the speed of a treadmill, with maximal hip extension eliciting a switch to flexor activity.[11,12] The extent to which CPGs are important in humans is debated,[7,13] though it is sadly all too clear from patients with complete spinal cord injury (SCI) that the putative human CPG is insufficient for locomotion, while remaining a potential target for regenerative therapies.[13–17]

Although the CPG can produce locomotor activity, successfully navigating an environment is only possible with supraspinal integration of sensory, visual, vestibular and contextual information and its transmission to the spinal cord. Subcortical regions higher up the chain of locomotor control include centres in the basal ganglia,[18,19] midbrain[18–22] and brainstem[18,23,24] which have been shown to be important in the initiation and modulation of locomotor behaviour. In most mammals, the neural circuity mentioned so far is sufficient to produce a remarkable range of locomotor behaviours, with decerebrate cats capable of modulating walking speed, pursuing targets and even learning new behaviours.[12]

Humans are unique in their development of habitual bipedalism and this has brought with it significant adaptations to the control of walking in our species. Whereas locomotion in quadrupeds places the centre of mass in front of the ground reaction force, bipedal walking necessitates the control of an inverted pendulum in the form of the trunk being propelled over the stance limb by the pushing-off of the swing limb.[25] It appears that the new demands of keeping this inherently unstable system upright, alongside the specialisation of the forelimb into an arm with a hand, led to a rapid rise in the importance of the motor cortex and corticospinal tract for all aspects of locomotor behaviour in humans. Ascending the phylogenetic tree from rodents to humans, corticospinal axons become larger and direct synapses on the motoneurons become the norm,[26] while the importance of the reticulospinal tract, particularly for distal limb control, and the rubrospinal tracts reciprocally decreases.[27] As a result, cortical stroke or interruption of the pyramidal tract results in a far more profound and lasting hemiparesis in humans than in most other mammals.[28]

It is not clear to what extent this cortical takeover of locomotor function in humans has left intact the subcortical and spinal locomotor mechanisms of our evolutionary past[29] – and, with them, potential means of eliciting recovery after neurological injury or disease, either through compensatory reorganisation of existing neural circuits or *de novo*, neuroplastic sprouting of axons from intact regions onto networks distal to a lesion.[30–35] Tantalising evidence for lumbar and cervical locomotor CPGs has been detected in healthy individuals and SCI patients.[15,36] However, the cortex is at least partially engaged in locomotor behaviours as seemingly automatic as arm swing, with transcranial magnetic inhibition of the motor cortex inhibiting rhythmic EMG activity in the proximal deltoid muscle.[37] Identifying and accounting for the differences in locomotor control across species – what has been preserved in the switch to bipedal gait and what has been lost – is important for the application and interpretability of animal models of locomotor function, damage and recovery.

Profiling locomotor function and recovery

Locomotor function in humans can be quantified and assessed in many ways, the simplest of which is to measure the speed at which an individual covers distance. While such measurements are straightforward and reproducible, they are incapable of distinguishing the specific underlying impairment from which gait disturbance arises, nor whether the subject relies on compensatory strategies.[38–40] Despite this disadvantage, timed completion of a set distance – including the timed 25ft walk[41,42] and the 10m walk test[43] – and distance completed in a set time – such as the 6min walk test – are the most widely used measures used in the evaluation of human gait and as clinical trial end-points.[44]

Three-dimensional (3D) kinematic gait analysis involves the use of multiple cameras to capture and reconstruct the 3D motion of a subject and extract parameters which describe the spatiotemporal aspects of gait and the movement of the individual joints and segments. It represents the gold standard in assessing locomotion and provides a means to discern the underlying mechanism of gait disturbance, allowing improved diagnosis, rehabilitation targeting and clinical trial stratification.[45–47]

Different types of motor behaviours varyingly utilise different neuroanatomical systems.[48–51] As a result, gait readouts during particular conditions may be more sensitive to lesions in different systems.[49] For instance, when the corticospinal tract is cut bilaterally in rats, the rubrospinal tract compensates for the lost distal forelimb function, but only during skilled reaching and not during locomotion.[48] Using 3D kinematic gait analysis, Zörner et al. profiled gait in rodents with a range of CNS lesions under several different locomotor conditions designed to place varying demands on the components of the locomotor system.[49] They demonstrated that wading, with proprioceptive feedback from the bottom of the tank and weight support through buoyancy, was more sensitive than swimming or overground walking in revealing residual stepping function in rats with damage to the reticulospinal and vestibulospinal tracts after ventral SCI. Similarly, rats with unilateral cervical hemisections showed normal hindlimb function when swimming or wading but impaired hindfoot placement became apparent when walking on a ladder.

Due to the neuroanatomical differences between species described earlier, directly applying this information to equivalent neurological lesions in humans is unlikely to yield many directly useful insights. However, leveraging the principle – challenging the neuroanatomical substrates of different locomotor behaviour – may lead to more sensitive markers of locomotor dysfunction and recovery in patients. A similarly comprehensive approach to the profiling of human gait has not yet been conducted, but insights from studies of walking while engaged in secondary tasks in healthy and locomotor-impaired humans suggests such dual-task paradigms may be more useful in discriminating clinically important differences in gait parameters than normal walking.[52–54]

The Stroop task as a means of modulating the cortical control of human gait

It has been known since the 1920s that presenting colour words in discordant colours and asking a participant to name the hue while suppressing the word leads to significantly longer reaction times and mental effort than when the colours are concordant.[55–57] The effect was later developed and popularised by John Ridley Stroop, after whom it is named.[58] Performance degrades with aging and in disorders affecting the cortex and white matter of the brain such as multiple sclerosis.[56,59–61] As cortical resources are finite, the distributed networks underpinning Stroop performance are thought to overlap and interfere directly with those responsible for gait control.[61–65] The effects of this interference are generally small, inconsistent across the literature and include decreased gait speed and changes in stride length and variability.[53] Interestingly, cadence control, thought to involve lower-order CNS circuits,[66,67] is unaffected by cognitive dual-tasks,[53] suggesting that the Stroop task may be a useful means to distinguish the components of walking governed by more distal, brainstem and spinal networks and those under more direct cortico-basal ganglia control.[68,69]

Visual restriction while walking as a means of challenging the tactile and proprioceptive systems

The observation that patients with impaired proprioception lose postural control in darkness was extensively described by Moritz Romberg between 1840 and 1846 and his eponymous test – in which patients are asked to close their eyes while standing and is positive if swaying or falling ensues – is now a cornerstone of clinical neurological assessment.[70,71] Applying the same

principle while walking is 76% sensitive for clinically significant cervical myelopathy[72] and visual restriction impairs toe obstacle clearance in patients with incomplete SCI.[73] Restriction of the lower visual field during treadmill walking is adequate to produce characteristic adaptation in toe clearance in healthy populations[74–76] and results in specific deficits in foot clearance in patients with peripheral neuropathy and dorsal column dysfunction.[73,77]

Profiling human gait: GaitPortfolio

Between 2013 and 2016, we developed, piloted and implemented a standardised protocol for the comprehensive profiling of treadmill walking in humans (clinicaltrials.gov; NCT02165787). This thesis focuses on condition-specific changes in kinematic gait parameters during normal walking, cognitive distraction using a modified Stroop task and a visual restriction task in which the lower half of the visual field is obscured. We recruited and measured 121 healthy participants and, to date, over 60 patients with neurological injuries and diseases. This thesis reports results from the control arm and data from patients with sensorimotor incomplete SCI.

Aims of the thesis

Studies in healthy participants

(Chapters 1 & 2)

To establish a human gait analysis paradigm in which healthy adults of all ages walk on a treadmill under varying locomotor conditions designed to challenge specific components of the human locomotor system.

Specifically, the effect of increasing levels of additional cognitive loading while walking will be investigated to gain insight into the influence of modulating supraspinal influence on key gait parameters, with emphasis on whether enhanced gait automaticity results. A restricted vision condition will also be employed, in which the non-visual sensory systems (somatosensory and proprioceptive) providing locomotor feedback are challenged.

Study in human spinal cord injury

(Chapter 3)

To utilise insights from Chapters 1 & 2 to apply an identical paradigm to patients with incomplete spinal cord injury. This section tests the hypothesis that cognitive loading has a greater effect on arm swing asymmetry in patients with thoracic injuries compared to those with cervical injuries due to the interruption of the propriospinal connections between the lumbar and cervical CPG components in the former group.

Case report in post-traumatic syrinx

(Chapter 4)

To demonstrate the application of newly-developed, tract-specific techniques, in this case contact-heat evoked potentials demonstrating sensitivity to lesions of the spinothalamic tract, in diagnosing and monitoring disorders of the spinal cord in humans.

Chapter 1: Minimum toe clearance: probing the neural control of locomotion

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Author contributions

TK designed the protocol, collected and analysed data, wrote the manuscript and prepared all figures.

1.1 Abstract

Minimum toe clearance (MTC) occurs during a highly dynamic phase of the gait cycle and is associated with the highest risk of unintentional contact with obstacles or the ground. Age, cognitive function, attention and visual feedback affect foot clearance but how these factors interact to influence MTC control is not fully understood.

We measured MTC in 121 healthy individuals aged 20 – 80 under four treadmill walking conditions; normal walking, lower visual field restriction and two Stroop colour / word naming tasks of two difficulty levels.

Competition for cognitive and attentional resources from the Stroop task resulted in significantly lower mean MTC in older adults, with the difficult Stroop task associated with a higher frequency of extremely low MTC values and subsequently an increased modelled probability of tripping in this group. While older adults responded to visual restriction by markedly skewing MTC distributions towards higher values, this condition was also associated with frequent, extremely low MTC values.

We reveal task-specific, age-dependent patterns of MTC control in healthy adults. Age-related differences are most pronounced during heavy, distracting cognitive load. Analysis of critically-low MTC values during dual-task walking may have utility in the evaluation of locomotor control and fall risk in older adults and patients with motor control deficits.

1.2 Background

Falls from standing height in adults over the age of 60 are associated with 1-year mortality as high as 33% and lead to considerable morbidity, reduced independence and financial burdens.[78,79] Trips may account for over half of falls in the elderly[80] and tripping over rugs or carpets alone resulted in 38000 adults over 65 being admitted to US emergency departments over 7 years.[81] Such trips during walking may result if insufficient clearance is maintained during swing phase to avoid uneven ground or unseen obstacles. The toe trajectory nadir that occurs at or very close to mid-swing, termed minimum toe clearance (MTC),[82–84] is the gait event associated with the highest risk of unintentional ground contact.[85,86]

Executive function and, more specifically, the ability to appropriately allocate attention to walking is increasingly regarded as crucial to gait control in healthy older adults, particularly under more challenging walking conditions.[87–94] Impairment of attentional control – the ability to appropriately allocate finite cognitive resources to information processing tasks[95] – is associated with an increased risk of injurious falls in older people.[96,97] The effect of additional cognitive load on MTC has been assessed both in overground and treadmill-based studies utilising various cognitive dual-task paradigms,[82,98–102] which report conflicting effects on mean or median MTC (generally small decreases or no change). Variability of MTC also appears to be controlled with high priority during cognitive dual-task walking[98,100] despite significant increases in that of other gait parameters.[53]

Although also cognitively demanding, walking with restricted vision appears to be associated with minimal gait adaptations in healthy older adults[103] and with a slightly increased mean MTC

relative to normal walking.[77,75,104] This discrepancy may be due to attention being consciously diverted *towards* walking during a restricted vision task, rather than *away* from it, as when performing an unrelated cognitive task, resulting in tighter, conscious control of MTC. Relying solely on changes in MTC mean / median or variability values to understand tripping risk and / or locomotor control under challenging walking conditions implicitly assumes normal distribution of MTC values. However, this is rarely the case in groups or individuals[99,75,105] and task-related shifts in frequency distribution may significantly increase an individual's tripping risk. Such aspects have only been partially explored.[85,101,105]

Based on these ideas, we developed a paradigm to investigate the effect of cognitive load and attention on the control of MTC in healthy adults of all ages. The conditions used – visual restriction and cortical distraction by means of a modified Stroop task – are complimentary in that the former encourages the participant to consciously attend to walking to ameliorate a challenge they are aware of, while the latter greatly distracts attention from locomotion. We additionally assess MTC distribution and timing and perform probability modelling to indicate the risk of tripping under cognitive load and restricted vision. We hypothesise that condition effects on MTC will be most pronounced in the group of adults aged over 60 and that the characteristics of MTC frequency distributions will result in higher modelled tripping risk in this group.

1.3 Methods

This two-centre study, carried out in accordance with the Declaration of Helsinki and Good Clinical Practice, was approved by the cantonal ethics committee of Zurich (KEK-2014/0004). Data were uploaded into a secure, tamper-proof clinical trials database (SecuTrial®, interActive Systems GmbH, Berlin, Germany). Healthy individuals were consecutively recruited via flyers and posters from the local area with a target of 20 males and 20 females in each of three, pre-defined age groups (20-39, 40-59, 60-80). All participants gave written, informed consent. Data collection was performed over two visits. In the first visit, participants underwent medical screening followed by a thorough neurological and orthopaedic examination and were excluded if any abnormality was detected, including colour-blindness. Upon inclusion, participants initially underwent 40 minutes of habituation on the treadmill during which they were familiarised with the test protocol. Subjects were blinded to the purpose of the study.

Participants returned 1-7 days later for gait analysis. The timed 25-foot walk test (T25FW) and the 10-metre walk test (10MWT) were performed simultaneously from a standing start in a hallway marked with both distances. The speed of the treadmill for all subsequent trails was set at 50% of maximal overground speed as a proxy for preferred treadmill velocity, defined as the mean velocity over two attempts at the T25FW. Motion capture (Vicon, Oxford, UK) was performed as participants walked normally on an instrumented treadmill (FDM-T, Zebris Medical GmbH, Germany) through which foot pressure data was also recorded at a sampling rate of 120Hz. A modified Cleveland model[106] (Motion Analysis Corp., Santa Rosa, CA, USA) reflective marker constellation was applied to the pelvis and lower limbs, with the great toe marker placed over the second metatarsal head. A standard Vicon Plug-in-Gait model was

applied to the upper body.[107] Vicon Nexus 1.8.5 motion capture software was used to record three-dimensional, kinematic data at 200Hz.

Stable gait was recorded over 30-45 seconds as participants walked barefoot on the treadmill without handrail support. Participants were asked to walk under four different conditions. For the baseline, normal walking condition (NW), participants walked while fixing their gaze on a 22" LCD monitor at eye height on which a cross was displayed (Figure 1.1a). Two levels of additional cognitive loading were achieved by means of a modified Stroop word/colour naming exercise[108] displayed on the same screen in place of the cross. In the first level (congruent Stroop; Figure 1.1b), colour-words (red, blue, green or yellow), written in a colour consistent with the word, were presented at pseudorandom intervals in the participant's self-declared native language and script. These intervals ranged between 600 and 1400ms around a mean frequency of 1Hz and the duration of a given stimulus was never within 200ms of the one preceding it. This modification of the standard Stroop task[58] was intended to avoid any entrainment of temporal gait parameters[109] and to encourage constant attention, as the participant could not predict stimulus duration. In the second, more difficult level (incongruent Stroop; Figure 1.1c), the word stimuli were presented in colours discordant with the written word. In both cases, participants aimed to state the colour in which the words were written as quickly and as accurately as possible.

In a fourth task, participants were asked to wear protective goggles which had been modified to obscure the lower half of the visual field (Figure 1.1d). This was achieved by affixing black fabric to the lower half of the goggles with Velcro® at the level of the individual's interpupillary line.

Participants again fixed their gaze on the central cross. Trials were repeated if participants used the handrails or failed to maintain a safe position on the treadmill.

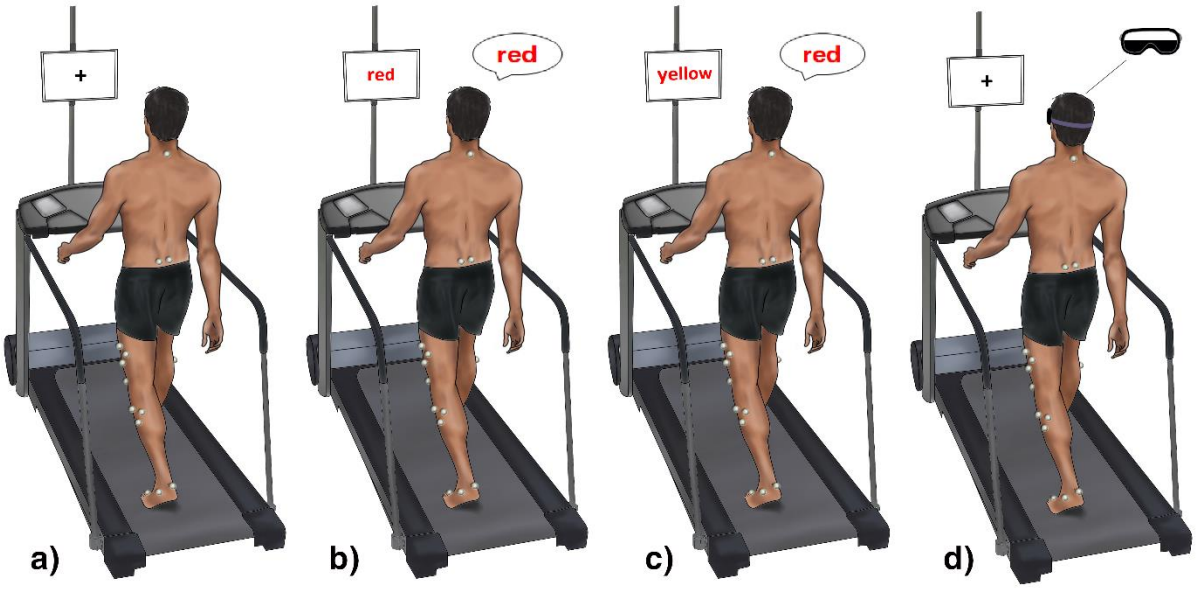


Figure 1.1. Experimental setup. Healthy adults aged 20-80 underwent 3D gait analysis while walking on an instrumented treadmill without handrail support. They undertook four locomotor tasks. Normal walking without a secondary task (a) was performed with the eyes fixed on a cross at eye height. Participants then walked while engaged in two Stroop colour-naming task (see methods) of differing difficulty. Image (b) shows the simpler task in which word and colour stimuli are congruent. In the more difficult, incongruent task (c) word and colour are discordant. Participants also carried out a visual restriction task in which they walked wearing eye goggles, the lower half of which were covered in black fabric to obscure the lower visual field. The upper edge of the fabric was affixed at the level of the subject's interpupillary line. This figure was adapted from Figure 1 in the publication Killeen et al. Increasing cognitive load attenuates right arm swing in healthy human walking. R. Soc. open sci. 2017 4 160993; DOI: 10.1098/rsos.160993. Published 25 January 2017 under the Creative Commons Attribution Licence 4.0.

Marker trajectories were reconstructed, labelled, filtered and modelled in Nexus 1.8.5. A custom Matlab script (The MathWorks, Natick, MA, USA) was used to set gait cycle events from the synchronised treadmill force-plate data with foot-strike and foot-off defined by downward and upward 5N threshold crossings respectively. Trials were manually inspected for recording and

processing errors before per-stride spatiotemporal gait parameters were calculated using Procalc 1.1 (Vicon). Specifically, MTC was defined as the minimum difference in the vertical axis between the left or right great toe marker during swing phase and its trial minimum during stance.

The individual whose photograph was used as the basis of Figure 1.1 was not a study participant and gave consent for the image to be published.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 (IBM Corp, Armonk NY, USA) and graphs produced using Prism 7.02 (Graphpad Software, La Jolla CA, USA). Attributes of the three age groups were compared using one-way ANOVA with post-hoc t-tests corrected for multiple comparisons with the Bonferroni method. The effect of locomotor condition on MTC and MTC timing, including the mean, median and coefficient of variation (CoV) of each parameter, were analysed using a linear mixed model in which condition (NW, congruent Stroop, incongruent Stroop, restricted vision) was a repeated measure. Fixed effects comprised condition, weight, height, age, gender and walking speed. Where significant condition effects were present, post-hoc t-tests were performed with Bonferroni correction and linear regression used to investigate relationships between scalar variables. Gait parameters of secondary interest, reflecting aspects of stability and gait control, were subjected to the same linear mixed model analysis. These comprised step width (+ coefficient of variation; CoV), step length (+ CoV) and the per-stride length of the 3D trajectory of the C7 marker and, to specifically assess mediolateral trunk sway, its 2D coronal component.

Analysis of MTC distributions was carried out by calculating the mean relative frequency of 1mm MTC bins for each age group. Each individual contributed MTC values for 25 strides to age group histograms. These data may also be presented as cumulative relative frequency plots by ordering all observations from smallest to largest. These distributions (i.e. 25x121 data points per histogram) were used for tripping probability modelling performed using a custom Matlab script based on the approach used by Best & Begg,[85] which takes into account skewness and kurtosis of the distributions to give the per stride probability of striking a hypothetical unseen object of a given size.

1.4 Results

One hundred and fifty-seven individuals volunteered to take part in this study. Thirty-six were excluded at initial screening due to abnormalities of the neurological or musculoskeletal system. The most frequent reason for exclusion was prior surgery to the lower limbs or spine. One hundred and twenty-one participants completed the full protocol. All individuals completed the normal walking and congruent Stroop trials. Data was unusable in two of the incongruent Stroop trials (both in the middle-aged group), while three older individuals were unable to complete the visual restriction trial safely. The remaining 479 trials were available for analysis.

There were no significant group differences in mean height or weight or gender distribution but older adults walked more slowly in the T25FW ($p \leq 0.020$) and 10MWT ($p \leq 0.010$) and covered less distance in the 6-metre walk test (6MWT; $p \leq 0.031$) than those in the younger age groups (Table 1). Accordingly, their mean fixed walking speed on the treadmill, set at 50% of the T25FW

speed, was also somewhat slower ($p \leq 0.040$). There were no significant differences between the younger and middle-aged groups.

During normal treadmill walking, mean MTC was 15.0mm (median 14.5mm) with a standard deviation of 4.0mm (interquartile range 2.1mm) for the whole cohort. There was no difference between the age groups in terms of MTC during normal walking, with values (mean ± SEM) of 15.1±0.5mm, 15.2±0.6mm and 14.5±0.5mm in the younger, middle-aged and older groups, respectively (Figure 1.2a). However, age differences did begin to become apparent during the cognitive dual-tasks, with older adults demonstrating significantly smaller MTC values than those aged 20-39 during the incongruent Stroop task (12.7±0.5mm *vs* 14.6±0.5mm; one-way ANOVA with post-hoc t-tests, $p=0.020$). There were no significant differences in MTC values across age groups during the visual restriction task. During both cognitive tasks, age was a significant, but weak, negative predictor of MTC, with R^2 values of 0.043 ($F=4.9$; $p=0.030$) in the congruent and 0.050 ($F=6.0$; $p=0.016$) in the incongruent Stroop tasks (Figure 1.3). During normal walking and visual restriction, no such relationship was observed.

Due to positively skewed distributions of most MTC histograms, median MTC values were generally marginally lower than the means but followed the same pattern with respect to condition-related changes. For completeness, these values are displayed in Supplementary Figure 1.1.

Condition effects on MTC and associated parameters

The trial minimum of the ipsilateral toe marker was used as the ground reference for determining MTC. Over all trials, the standard deviation of this value with respect to position of this marker relative to the treadmill frame during normal walking was 1.12mm in the vertical axis. This variability was not significantly different across age groups or walking conditions.

Locomotor condition ($p<0.001$) was among four parameters revealing significant main effects on MTC within the linear mixed model. The others were gender ($p=0.037$), weight ($p=0.004$) and walking speed ($p=0.000$). Post-hoc linear regression during normal walking revealed that walking speed was a weak, yet significant, positive predictor of MTC (R^2 0.121; $F=17.1$; $p=0.000$).

Corrected, post-hoc comparisons revealed that, under the congruent Stroop task, MTC decreased significantly relative to normal walking (Fig. 1.2b) in the middle-aged (13.2±0.4mm; $p=0.030$) and older groups (12.6±0.4mm; $p=0.016$). A similar reduction in MTC was seen during the incongruent Stroop in the older age group (12.7±0.5mm; $p=0.050$). Generally, visual restriction was associated with a rebound of MTC to mean values similar to those of normal walking, with MTC during visual restriction significantly higher than that in both cognitive tasks in middle-aged (16.4±0.6mm; $p\leq0.002$) and older adults (17.2±0.9mm; $p\leq0.004$).

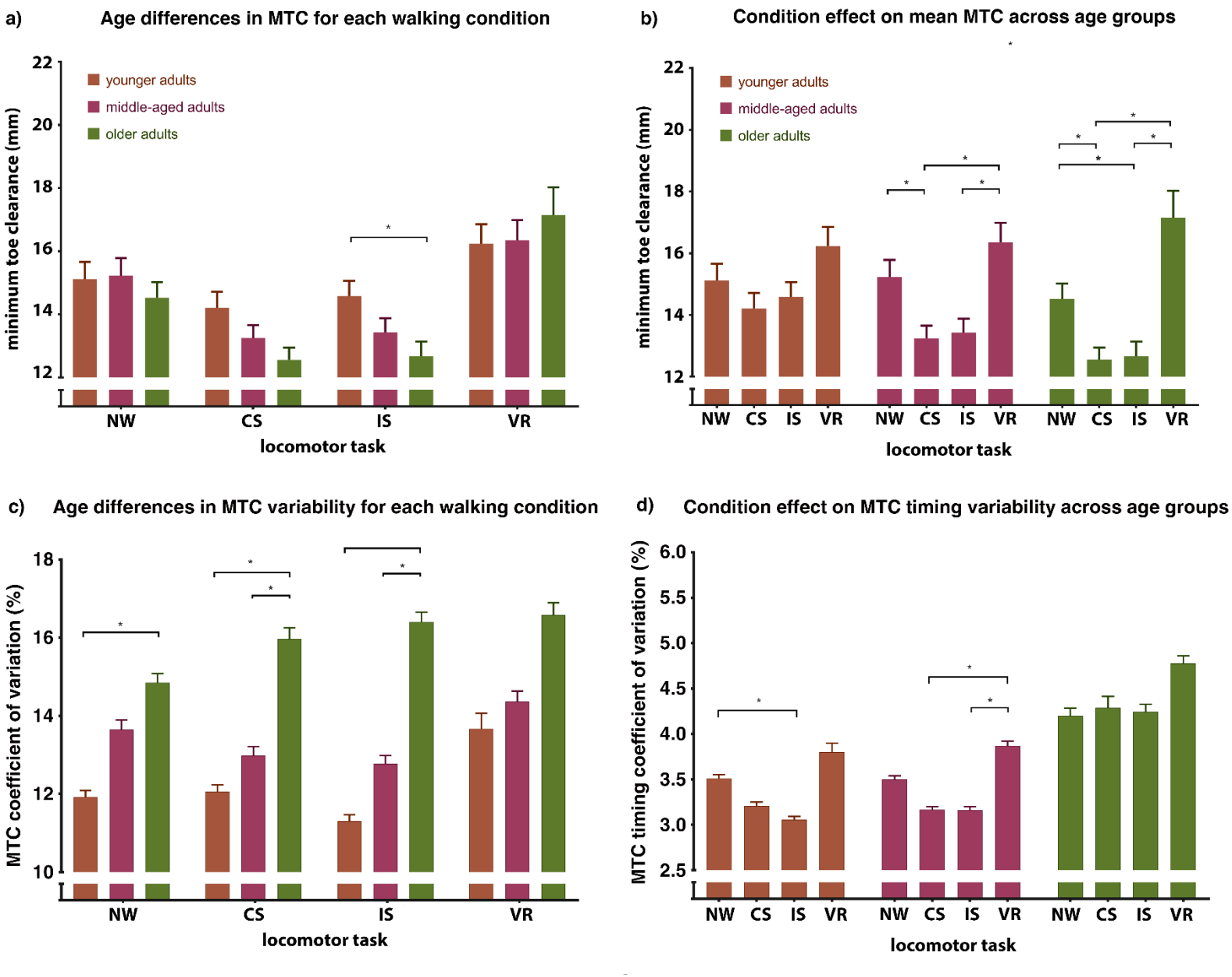
In older adults, MTC CoV was significantly higher compared to that of younger adults in all tasks except visual restriction (ANOVA with post-hoc t-tests; $p\leq0.032$, Fig. 1.2c). No group showed any significant task-related changes in overall MTC CoV.

Absolute timing of MTC did not vary significantly between age groups or under the different walking conditions within age groups (data not shown), with MTC occurring at 57±3.6% (±SD) of swing phase in the overall cohort. Stride-to-stride variability of this metric did show some significant changes, with MTC timing coefficient of variation (CoV) reduced in younger adults during the incongruent Stroop task (mean ± SEM; 3.51±0.13% vs 3.06±0.11%; p=0.049). In the middle-aged group, MTC timing CoV increased with visual restriction (3.87±0.17%) relative to both Stroop tasks (congruent; 3.17±0.11%; p=0.02, incongruent; 3.16±0.12; p=0.002, Fig. 1.2d). Older adults showed no significant condition effect, but had significantly greater MTC timing variability compared to both younger groups in all locomotor tasks (data in Fig. 1.2d, p≤0.04; comparisons not shown).

Age group	n	Age (years)	Percent female	Weight (kg)	Height (cm)	Walking speed (kmh^{-1})	T25FW (s)	10MWT (s)	6MWT (m)
Young (20-39)	41	29.1±5.0	51.2	70.1±14.5	172±8	4.15±0.60	3.37±0.45	4.41±0.63	724±74
Middle-aged (40-59)	40	47.7±6.0	50	72.6±15.5	172±9	4.01±0.52	3.49±0.47	4.60±0.59	710±77
Older (60 – 80)	40	67.5±6.0	47.5	68.6±11.9	169±8	**3.69±0.56**	**3.79±0.52**	**4.95±0.73**	**664±90**

Table 1.1. Demographics and walking ability in the three age groups. Group comparisons were made using one-way ANOVA with post-hoc t-tests corrected for multiple comparisons (Bonferroni). Values given are means ± standard deviation. Bold type indicates significant difference compared to both other age groups at the p≤0.05 level. T25FW; timed 25-foot walk, 10MWT; 10-metre walk test, 6MWT; 6-minute walk test.

Figure 1.2 (next page). Minimum toe clearance parameters under dual-task locomotor conditions. a) The effect of age group on MTC in each of the four walking conditions. Differences in mean MTC between age groups (younger adults; 20-39, middle-aged adults; 40-59, older adults; 60-80) tested using ANOVA and post-hoc t-tests where appropriate with significance set at $p \leq 0.05$, corrected for multiple comparisons (Bonferroni). NW; normal walking, CS; congruent Stroop task, IS; incongruent Stroop task, VR; visual restriction. b) Within-age group condition effects on mean MTC, compared using a linear mixed model (see methods) and post-hoc t-tests where appropriate with significance set at $p \leq 0.05$, corrected for multiple comparisons (Bonferroni). c) Differences in mean MTC variability (coefficient of variation; CoV) between age groups, compared using ANOVA as in a). d) Condition effect on MTC timing variability (CoV), compared using a linear mixed model as in b). Error bars indicate SEM.


a)
Age differences in MTC for each walking condition
younger adults
middle-aged adults
older adults
minimum toe clearance (mm)
22
20
18
16
14
12
NW
CS
IS
VR
locomotor task
b)
Condition effect on mean MTC across age groups
younger adults
middle-aged adults
older adults
minimum toe clearance (mm)
22
20
18
16
14
12
NW CS IS VR NW CS IS VR NW CS IS VR
locomotor task
c)
Age differences in MTC variability for each walking condition
MTC coefficient of variation (%)
18
16
14
12
10
NW
CS
IS
VR
locomotor task
d)
Condition effect on MTC timing variability across age groups
MTC timing coefficient of variation (%)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
NW CS IS VR NW CS IS VR NW CS IS VR
locomotor task

Condition effects on MTC frequency distributions

None of the group MTC histograms were normally distributed, with all demonstrating positive skewness and all but one (visual restriction in adults aged 40 – 59) were leptokurtic (Figure 1.4 and Supplementary Figure 1.2). Visual restriction resulted in a histogram shifted towards higher MTC values, with marked increases in skewness. Conversely, lower MTC values and decreased kurtosis and skewness were associated with the Stroop tasks. Cumulative relative frequency plots of the four walking conditions for each of the three age groups are displayed in Figure 1.5. While in younger and middle-aged adults there was little difference in the distribution of MTC values under the two levels of the Stroop task, in older adults a dissociation was observed, with the more demanding, incongruent Stroop task associated with notably higher frequencies of extremely low MTC values (below 10mm; Figure 1.5).

Tripping probability modelling yielded curves derived from each group histogram (Figure 1.6 and Supplementary Figure 1.2a, b). In older adults, all walking conditions were associated with a higher risk of tripping over hypothetical, unseen objects of all heights compared to that of the two younger groups (Supplementary Figure 1.3). Both Stroop tasks were associated with elevated tripping risk relative to normal walking in all ages. In the older age group, the dissociation of the frequency distributions at extremely low MTC values under the different levels of cognitive distraction manifests as markedly higher tripping risk during the more demanding of the two Stroop tasks below 10mm (Figure 1.6). Data for one individual was removed from the younger age group for the calculation as inclusion of this data caused the probability modelling for the incongruent Stroop task to fail, likely because the distribution pattern was biphasic.

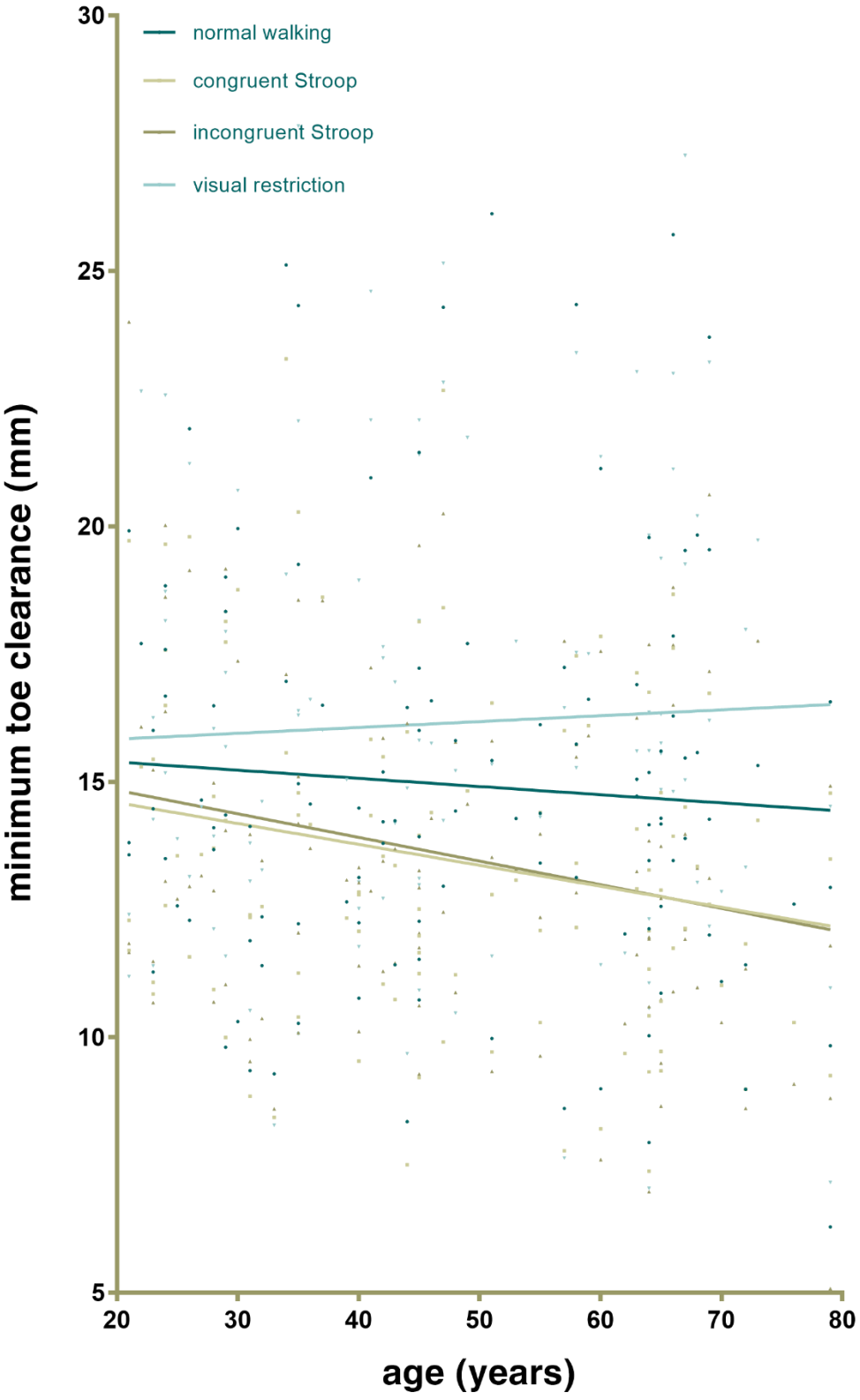
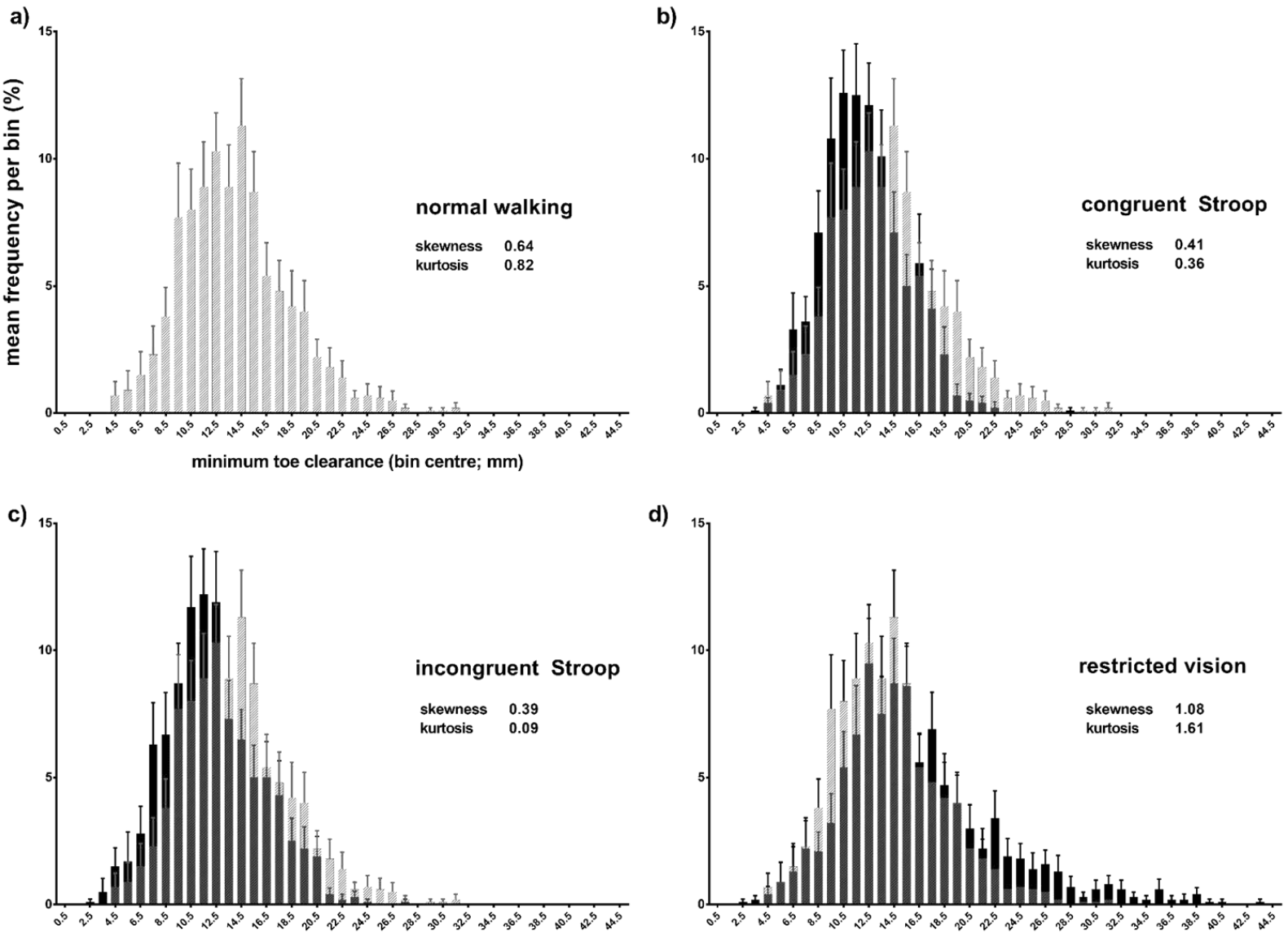

normal walking
congruent Stroop
incongruent Stroop
visual restriction
minimum toe clearance (mm)
30
25
20
15
10
5
20
30
40
50
60
70
80
age (years)

Figure 1.3 (previous page). Scatter plot of age and mean minimum toe clearance under four walking conditions. During the congruent and incongruent Stroop tasks, age was a significant, but weak, negative predictor of MTC, with R^2 values of 4.3% (F=4.9; p=0.030) in the congruent and 5.0% (F=6.0; p=0.016) in the incongruent task. During normal walking and visual restriction, no such relationship was observed.

Figure 1.4 (next page). Relative MTC frequency distributions for healthy adults aged 60-80 years. Each individual contributed MTC values for 25 consecutive strides. Values indicated are mean frequencies per 1mm bin with error bars indicating standard error of the mean. The histogram for normal walking is indicated in (a) and is presented as a semi-transparent overlay (grey) to allow comparison with the histograms of the three locomotor conditions (black; b-d). Similar graphics for the younger and middle-aged cohorts may be found in the supplementary material.


Relative frequency distribution for each walking condition in older adults (60-80 years)
a)
mean frequency per bin (%)
normal walking
skewness 0.64
kurtosis 0.82
minimum toe clearance (bin centre; mm)
b)
congruent Stroop
skewness 0.41
kurtosis 0.36
c)
incongruent Stroop
skewness 0.39
kurtosis 0.09
d)
restricted vision
skewness 1.08
kurtosis 1.61

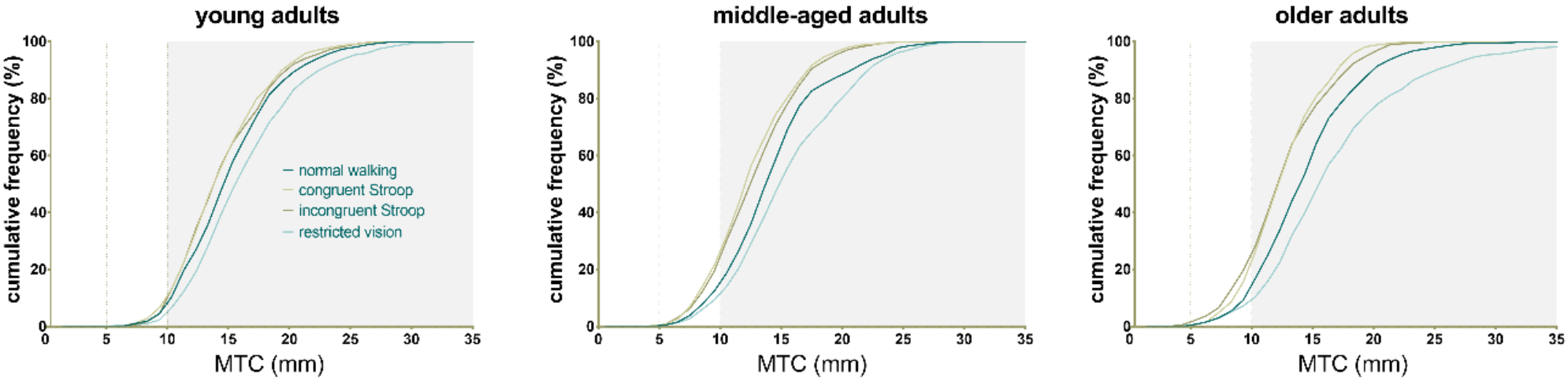


Figure 1.5. Minimum toe clearance cumulative relative frequency graphs for each age group. Each individual contributed 25 consecutive MTC values to the group histogram. Dotted lines indicate MTC thresholds of 5mm and 10mm, while shaded area indicates MTC values over 10mm. MTC; minimum toe clearance.

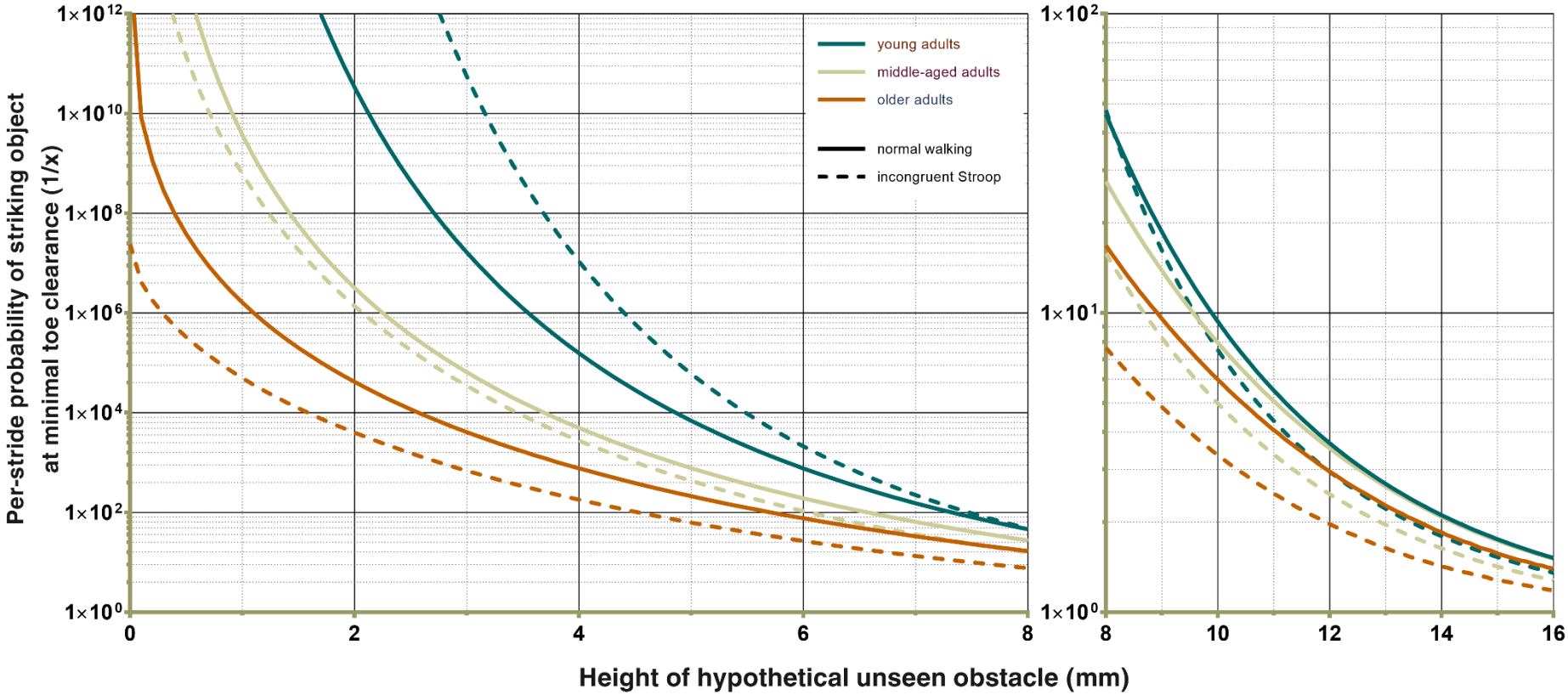


Figure 1.6. Tripping probability modelling for healthy adults aged 20-80 years during normal walking and under increased cognitive load. Modelling was based on the group frequency distributions and followed the approach taken by Best and Begg.[88] Briefly, per-stride probabilities of striking a hypothetical, unseen obstacle of a given height at MTC are modelled based on MTC frequency distributions, including skewness and kurtosis. Similar graphics for all conditions and age groups may be found in the supplementary material.

1.5 Discussion

The search for unequivocal gait markers of tripping risk in older adults and patients with impaired locomotion has been frustrated by high inter- and intra-individual variability of candidate parameters or low specificity.[110,111] Here we demonstrate that a combined analysis of the response of MTC to different locomotor conditions, including distribution analysis, is feasible and capable of revealing age-dependent and task-specific differences in motor control mechanisms in a large cohort of healthy adults.

MTC is predominantly mediated by dorsiflexion at the ankle joint around mid-swing[112] and it is thought that tibialis anterior is under more direct corticospinal control than the extensors active in early swing phase.[113–115] Thus, it is reasonable to anticipate kinematic adaptations to changes in the degree of supraspinal control of walking to manifest in attributes of MTC. The results presented here are compatible with a simple hierarchical model of motor control,[116,117] in which depletion of attentional resources by the Stroop task causes a shift towards a more autonomous, self-organised gait pattern characterised by reduced MTC, a less skewed MTC distribution and perhaps reduced variability.[117] On the other hand, restricting vision encourages the effortful intervention of higher levels of the CNS, resulting in kinematic adaptations aimed at reducing the likelihood of floor contact.

At 15.0mm, the mean MTC during normal treadmill walking in this study was similar to central tendency values at preferred speed reported previously (14.9 – 15.6mm).[83,99,105] Also in line with previous work, no significant differences in baseline (i.e. normal walking) MTC were observed between age groups.[99] There is no ideal measure of central tendency for invariably non-

normally distributed MTC data. We chose the mean as our main descriptor for two reasons: the number of gait cycles (25) was relatively low, meaning the median is susceptible to sampling fluctuations and the mean is reported more frequently in the MTC literature, allowing comparisons. Due to the positive skewing of nearly all histograms, median MTC was nearly always somewhat smaller than the corresponding mean. We report the median values for the main findings in Supplementary Figure 1.1.

As expected, condition effects were most pronounced in the healthy elderly, with significant decreases in MTC under cognitive load and a trend towards elevated values under visual restriction. These results corroborate both the tendency towards small MTC decreases observed during diverse dual-task experiments (answering questions,[118] serial subtractions)[98] and MTC increases during visual blurring or restriction.[75,119] In keeping with earlier research, MTC CoV during normal walking showed a significant increase with age[99,105] yet was not significantly modified by cognitive loading[98] or visual restriction.[77] This suggests that a strategy of reducing overall MTC variability to minimise critically low MTC values described elsewhere[100] is not, in fact, utilised by healthy adults under increased cognitive load. Other spatiotemporal parameters were remarkably insensitive to the different conditions, although a significant increase in upper body sway was observed during the Stroop tasks in the elderly. This may be related to postural instability, an artefact of articulation during the task[95] or may be related to increased arm swing asymmetry, which is known to result from engaging in the Stroop task.[120]

Aging is associated with recruitment of a broader range of brain structures during gait control compared to younger adults, particularly the prefrontal and basal ganglia networks[39,40] that also

represent the neural substrate of Stroop task performance.[11,38,41,42] When attentional resources are consumed by the relatively mild cognitive demands of the congruent Stroop task, the elderly CNS produces a narrower range of MTC values. While overall CoV is barely affected, a marked deskewing away from higher MTC values is seen (Figure 1.4b), and kurtosis decreases towards 0, i.e. a more normal distribution. This is possibly an attempted safety strategy utilising preserved peripheral visual cues,[104,105] although it is difficult to see the utility of eliminating high outlier MTC values with the small yet significant drop in mean MTC and the attendant increase in tripping risk. Instead, this move towards a suboptimal, normal distribution are most compatible with a switch to a more stereotyped, automated motor control strategy dominated by the brainstem and spinal cord as higher attentional resources are directed to the Stroop task.[53] Despite this, during the *congruent* Stroop task, older adults maintain enough attentional control to minimise extremely low, dangerous MTC values. When cognitive load is increased further in the more difficult, *incongruent* task, however, supraspinal processing of visual and sensory afferent information competes for limited attentional resources and the influence of the brainstem and spinal cord systems on the locomotor pattern increase at the expense of higher levels of control.[117] In younger adults, this lower-order system is capable of producing safe MTC parameters.[100] During healthy aging, however, this mechanism may gradually become less reliable due to a switch towards the prioritisation of balance,[121,122] degradation of the afferent pathways on which rhythmic spinal centres depend[123] or a general reduction in gait automatism in old age,[92,63,117] to the degree that potentially critical MTC events occur (Figure 1.4c).

Visual restriction, in which attentional resources are freely available yet feedback is degraded, results in a converse strategy that is imperfectly implemented by older adults, the locomotor

system compensates by amplifying skewness towards higher MTC values (Figure 1.4d). In contrast to the more automatic pattern under cognitive load, walking without visual feedback results in highly skewed MTC distributions in keeping with cautious, tight control of MTC reliant on the other senses available to the CNS.[77,124] Unlike cognitive distraction, participants were keenly aware that their locomotor system was being challenged and likely switched conscious attention to control of MTC. Perhaps once more due to impaired proprioception and/or descending motor control in older adults, the frequency of extremely low MTC values increases despite this strategy of tighter control and tripping risk rises.

While changes in mean MTC and variability in all tasks were small in absolute terms, probability modelling of the group histograms show that the changes in MTC distribution characteristics brought about by secondary tasks can have substantial effects on the theoretical risk of tripping. MTC values ≤ 10mm at the left of the distribution curve have profound consequences. For an unseen, 4mm obstacle conflicting with MTC, the per-stride risk of tripping for a young adult walking normally with no dual-task is approximately 1:15000, while for a healthy, older individual engaged in a demanding cognitive task, the same scenario is associated with a 1:180 risk of contact (Figure 1.6). To perform meaningful comparisons of these modelled risks, studies including cohorts of patients and elderly individuals with a history of falls are required to determine cut-offs or odds ratios that indicate increased fall-risk.

Only one study has examined MTC timing under dual-task conditions. In our cohort, mean MTC timing was entirely resistant to dual-task effects, confirming the findings of Santhiranayagam et al.[100] Interestingly, variability of MTC timing was the only parameter to undergo any significant adaptation in healthy young adults, with a significant reduction seen during the more

demanding, incongruent Stroop task. This effect lost significance in the middle-aged cohort and disappeared entirely in healthy older adults, in whom MTC timing was high relative to young adults across all tasks (Figure 1.2d). These are unexpected results, as cognitive / locomotor dual-task effects are usually more pronounced in older adults.[53] They are also in contrast to findings in the spatial MTC variability domain in this study (Figure 1.2c), in which MTC height variability was unaffected by walking task, and imply different control mechanisms.[125] Temporal aspects of gait, including MTC timing, may be more readily delegated to subcortical, brainstem and spinal locomotor components in the event of attentional resources being reallocated to a secondary task,[53,67] resulting in more constrained MTC timing. As MTC timing is considerably less critical to tripping risk than toe clearance itself, this trade-off is beneficial in a dual-task setting.

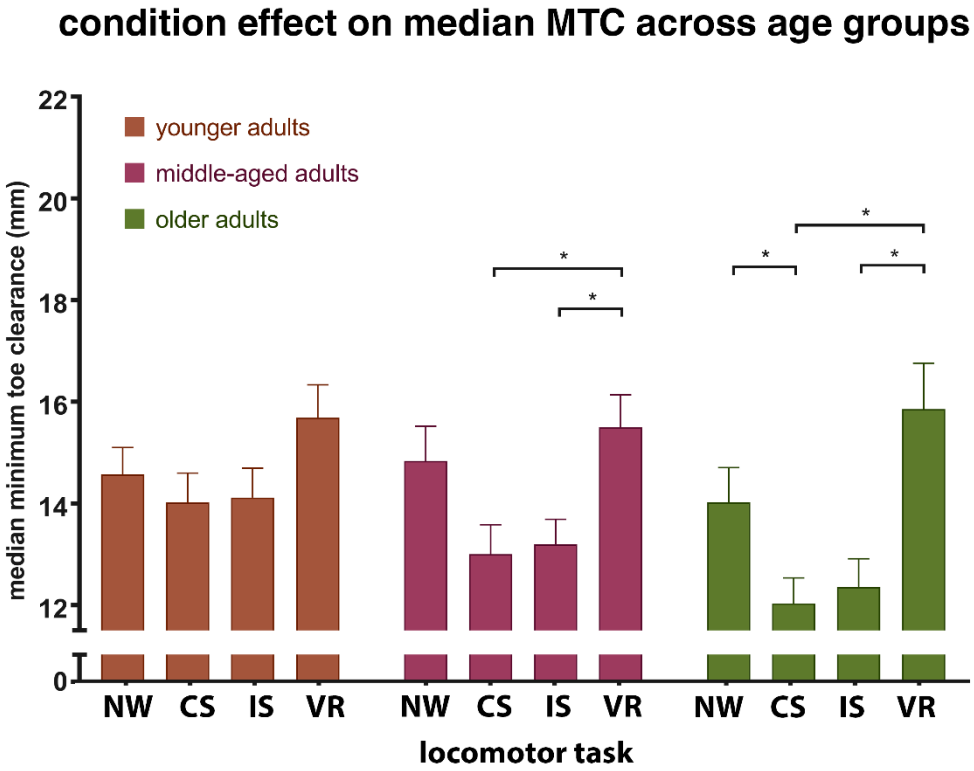
There is large heterogeneity in the design and conduct of cognitive dual-task paradigms in gait analysis.[53] Most approaches include rhythmic stimuli and / or verbal responses which may entrain cadence or other spatiotemporal gait parameters and confound condition effects.[109,126,127] Furthermore, anticipation of intervals between stimuli allows participants the opportunity to revert their attention and cognitive resources to walking, resulting in a fluctuating and unpredictable degree of cognitive load. The modified Stroop task employed here aims to ameliorate these issues and provide a constant level of attentional and cognitive distraction. In this study, treadmill walking speed was set at 50% of each individual's maximal overground walking speed. We employ this objective speed-selection approach in the clinical setting, as it allows us to challenge participants with dissimilar walking abilities to a proportional degree, irrespective of the many factors which may influence preferred treadmill speed.[108,128] Healthy

participants of all ages and body types thus walked at a speed that was proportional to their walking ability and which all perceived as comfortable. The small yet significant difference in absolute walking speeds between age groups (Table 1) may potentially influence MTC; indeed, higher walking speeds are associated with increased MTC values.[112,129] In an overground study of unilateral transtibial amputees, intra-individual increases in walking speed from 0.97 to 1.36 m/s resulted in a 2.9mm increase in MTC.[112] We believe such an inter-group effect of walking speed to be minimal in our sample, as the absolute difference in speed was small (0.14m/s) and there were no significant differences in MTC between age groups during normal walking.

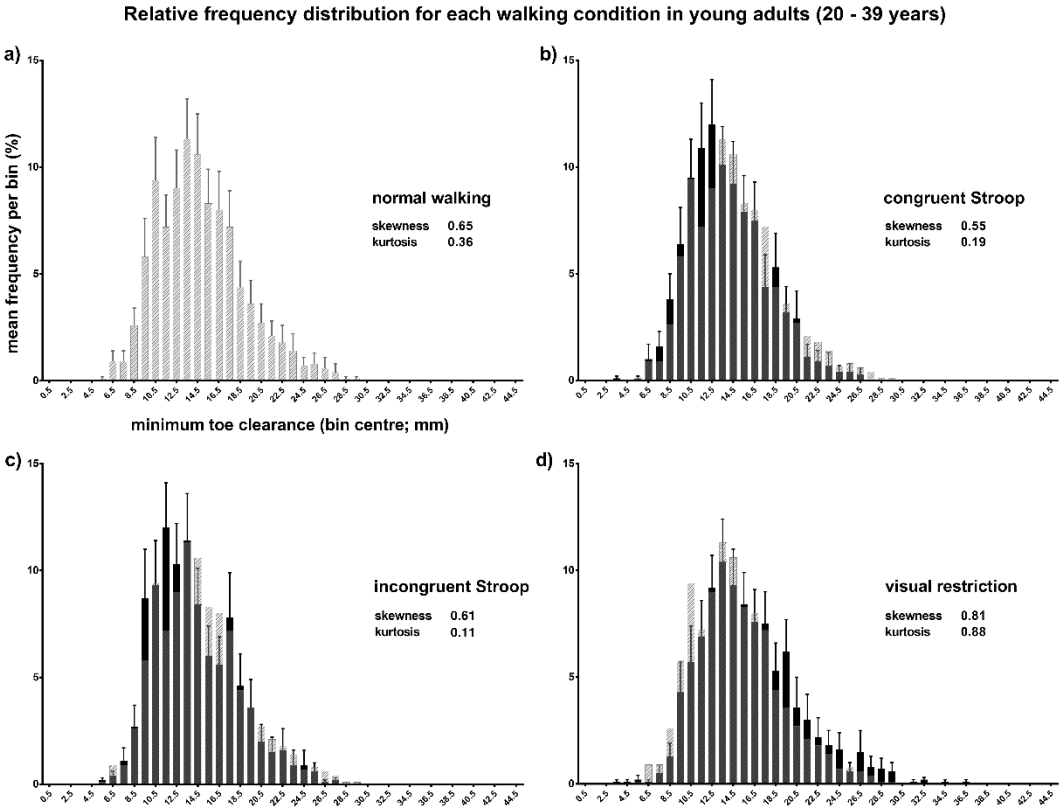
This study used group histograms to characterise MTC distribution and model tripping risk based on an established approach.[85] Caution should be exercised in interpreting the results of the probability modelling as the approach assumes that the hypothetical object will remain unseen and that it passes under the foot at MTC and not at any other point of swing phase. These “risks” should thus be seen as relative to one another and not indicative of absolute likelihoods, which are subject to myriad factors. Importantly, we did not consider heel clearance which is usually closer to the ground than the toe during the last third of the swing phase.[130] As heel height reaches zero at heel-strike, determining a meaningful heel clearance parameter that relates to tripping (i.e slipping) risk in this phase is difficult and beyond the scope of this paper. Our main aim was to provide norm data against which patients with neurological injury and disease may be compared during clinical, treadmill-based gait analysis. Translating these findings to overground walking should be done with caution as variability parameters are known to differ significantly between treadmill and overground walking.[131] Overground MTCs may generally be smaller[118] and MTC increases under lower visual field restriction may be more

marked on the treadmill due to the absence of optic flow or the view of the path ahead as additional compensatory cues.[75] While we used a sophisticated gait analysis system, MTC is a relatively simple parameter to calculate and can be measured using affordable systems in a clinical setting.[132] Future work should concentrate on characterising MTC values under dual-task conditions in patients and older adults known to be at risk of falling. This should include analysis of distribution and the frequency of extremely low MTC values. Such an approach may yield sensitive and specific gait biomarkers for neurological walking disorders, specific lesions and fall risk.

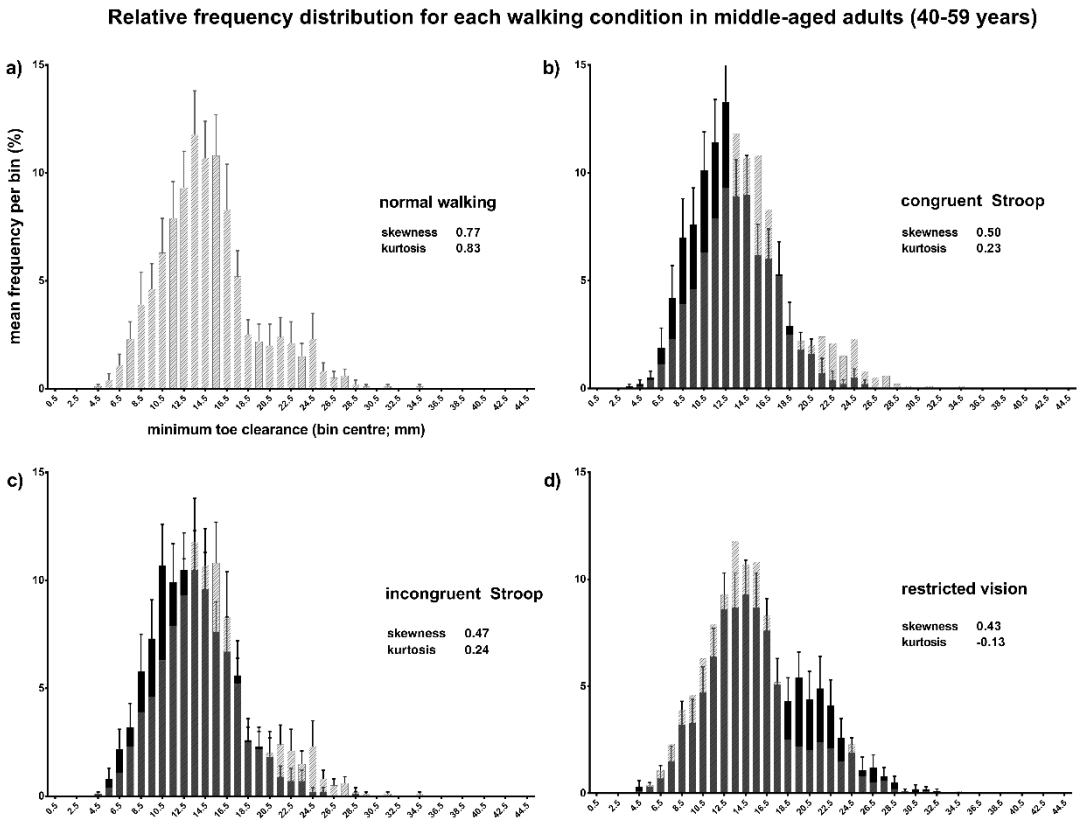
Here we provide comprehensive toe clearance data for adults free of orthopaedic or neurological disease walking on a treadmill. The findings suggest that the analysis of low outlier MTC values, rather than mean MTC, during dual-task treadmill walking may be a useful indicator of motor control ability, including fall risk, in older adults. Application of this approach to other populations with impaired motor control, such as patients with brain and spinal cord lesions, may also prove to be a sensitive gait biomarker for rehabilitation and other treatments designed to improve locomotor control in these groups.



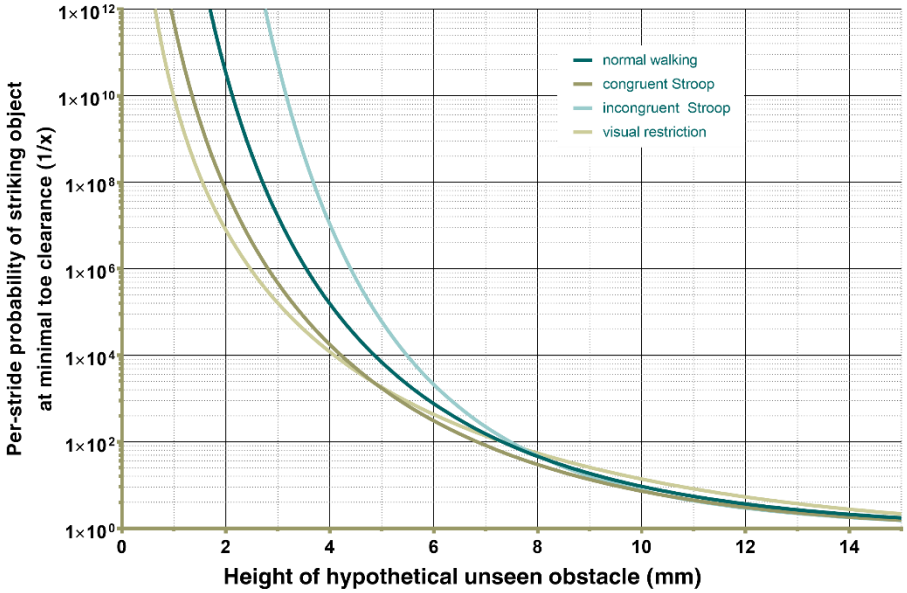
Supplementary Figure 1.1. Median minimum toe clearance under different locomotor conditions. Within-age group condition effects on median MTC, compared using a linear mixed model (see methods) and post-hoc t-tests where appropriate with significance set at $p \leq 0.05$, corrected for multiple comparisons (Bonferroni). Error bars indicate SEM. NW; normal walking, CS; congruent Stroop task, IS; incongruent Stroop task, VR; visual restriction.



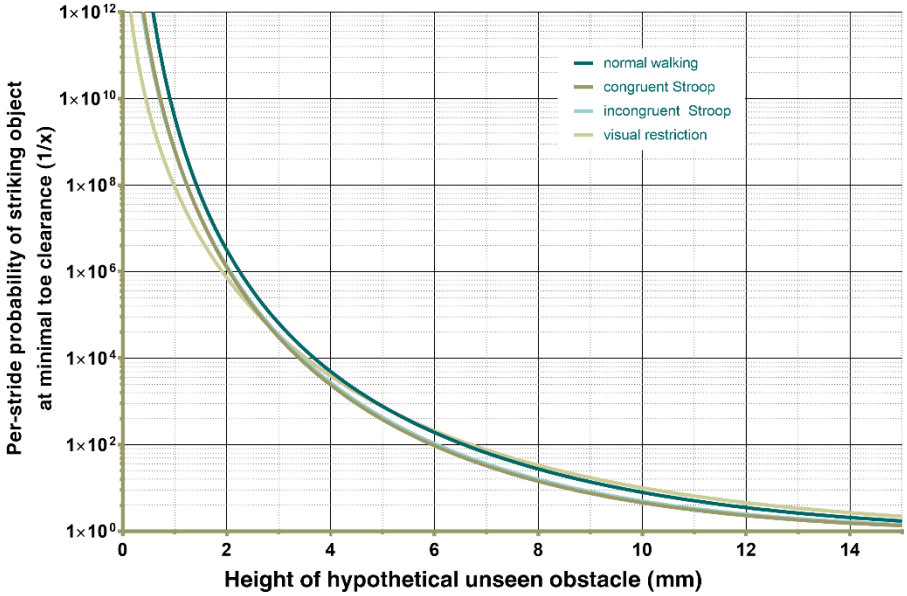
Supplementary Figure 1.2a. Relative MTC frequency distributions for healthy adults aged 20-39 years. Each individual contributed MTC values for 25 consecutive strides to the group histogram. Mean values are given as mean frequencies per 1mm bin with error bars indicating SEM. The histogram for normal walking is indicated in (a) and is presented as a semi-transparent overlay (grey) to allow comparison with the histograms of the three locomotor dual tasks (black; b-d).



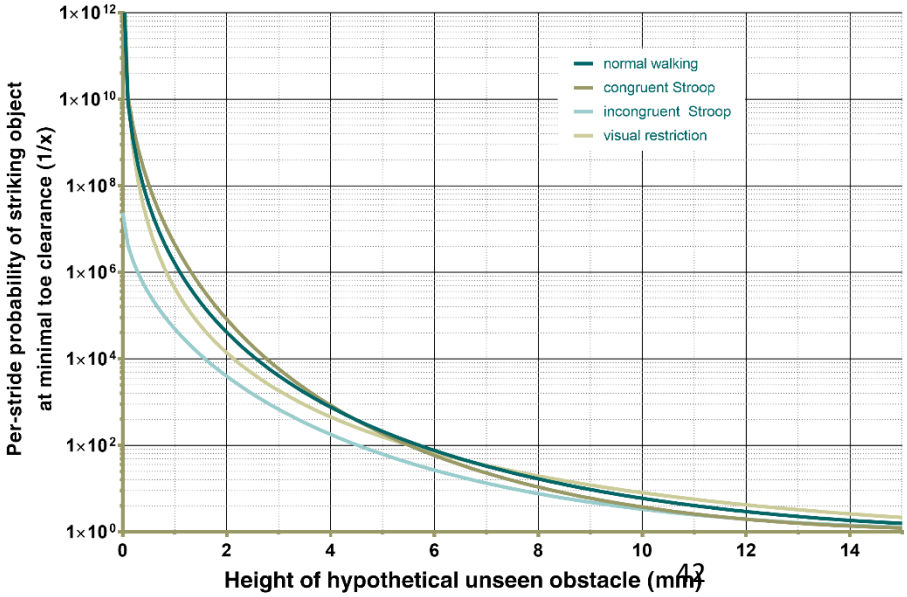
Supplementary Figure 1.2b. Relative MTC frequency distributions for healthy adults aged 40-59 years. Each individual contributed MTC values for 25 consecutive strides to the group histogram. Mean values are given as mean frequencies per 1mm bin with error bars indicating SEM. The histogram for normal walking is indicated in (a) and is presented as a semi-transparent overlay (grey) to allow comparison with the histograms of the three locomotor dual tasks (black; b-d).



younger adults



middle-aged adults



older adults

Supplementary Figure 1.3 (previous page). Tripping probability modelling for (upper) healthy adults aged 20-39 years, (middle) 40-59 years and (lower) 60-80 years under different locomotor conditions. Modelling was based on the group frequency distributions and followed the approach taken by Begg et al.6 Briefly, per-stride probabilities of striking a hypothetical, unseen obstacle of a given height at MTC are modelled based on MTC frequency distributions, including skewness and kurtosis.

Chapter 2: Increasing cognitive load attenuates right arm swing in healthy human walking.

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Author contributions

TK designed the protocol, collected and analysed data, wrote the manuscript and prepared all figures.

2.1 Abstract

Human arm swing looks and feels highly automated, yet it is increasingly apparent that higher centres, including the cortex, are involved in many aspects of locomotor control. The addition of a cognitive task increases arm swing asymmetry during walking, but the characteristics and mechanism of this asymmetry are unclear. We hypothesised that this effect is lateralised and a Stroop word-colour naming task – primarily involving left hemisphere structures – would reduce right arm swing only.

We recorded gait in 83 healthy subjects aged 18-80 walking normally on a treadmill and while performing a congruent and incongruent Stroop task.

The primary measure of arm swing asymmetry – an index based on both three-dimensional wrist trajectories in which positive values indicate proportionally smaller movements on the right – increased significantly under dual-task conditions in those aged 40-59 and further still in the over-60s. This was driven by reduced arm flexion, supporting findings that limb flexors are under more direct supraspinal control.

Right arm swing attenuation appears to be the norm in humans performing a locomotor-cognitive dual-task, confirming a prominent role of the brain in locomotor behaviour. Women under 60 are surprisingly resistant to this effect, revealing unexpected gender differences atop the hierarchical chain of locomotor control.

2.2 Background

At all walking speeds, arm swing in human gait is driven at least partially by muscle activity.[133–135] While spinal central pattern generator (CPG) networks are implicated in arm swing generation and maintenance,[36,135,136] recent evidence also supports a motor cortex contribution via the corticospinal tract.[37] Dual-task experiments, in which healthy participants walk while engaged in a secondary, cognitive task, have been observed to result in changes in the degree of arm swing amplitude relative to that of the contralateral arm – and thus the symmetry of the two movements. [108,137–139]

The large majority of studies investigating arm swing symmetry examine the effect of walking conditions or disease states on an absolute arm swing symmetry index (ASI) calculated from a range of base parameters including sagittal shoulder angles or wrist trajectories, with most indices a variation on this calculation, in which L is the parameter of interest (e.g. sagittal shoulder angle) on the left and R that on the right:

$$ABS\ (ASI = \left(\frac{L-R}{max(L,R)}\right) \times 100)$$

which gives a scale of 0 (symmetrical) to 100 (maximally asymmetrical). Importantly, such metrics are agnostic to the direction of asymmetry and, as such, preclude the study of lateralised effects. When lateralised effects are sought, the absolute term is dropped, giving a scale of -100 (maximal right-dominant asymmetry) to 100 (maximum left-dominant asymmetry), with 0 representing perfect symmetry:

$$ASI = \left(\frac{L-R}{max(L,R)}\right) \times 100$$

Intriguingly, studies of healthy walkers consistently describe a tendency for arm swing movements to be larger on the left [8,10–12]. Plate et al recently investigated the effect of a serial subtraction task and a Stroop colour/word naming task during treadmill walking. While their main interest was absolute asymmetry changes, they noted that the Stroop task was associated with significantly more left-lateralised arm swing in healthy older walkers than the subtraction task.[138] We observed a similar tendency in a group of 12 young, healthy subjects

walking on a treadmill while performing the Stroop task.[108] It remains, however, unclear whether a reduction in right arm swing amplitude or an increase on the left is responsible for these changes. The Stroop task, in which a participant must state the colour in which a colour-word is presented while suppressing its conflicting, written form, depends upon a number of brain structures critical for cognitive control, including prefrontal, cingulate and basal ganglia networks, [61,62,140,141] some of which are also common to the control of gait [63,64,122,142] and arm swing.[139,143] As the Stroop task is predominantly a language exercise, its neural substrates are understood to be substantially lateralised, with left hemisphere structures activated more strongly than those on the right.[61,144] Cognitive-motor interference primarily in the left brain may therefore be responsible for the observed lateralised effect of the Stroop task on arm swing. While cognitive dual tasks, including the Stroop task, have been shown to have bilateral effects on lower limb kinematics[53], similar, unilateral effects either do not arise in the legs or are compensated for due to the need for maintaining symmetry for forward progression. The lumbar CPG may also be less susceptible to modulation of supraspinal influence than its cervical subsidiary involved in rhythmic arm movements.[36,145,146] In contrast to lower limb locomotor movements, arm swing may marginally increase the efficiency of gait but is not necessary for walking[134,147] and thus it is reasonable to assume that a lateralised response to interference from unilateral cognitive loading is more likely to manifest here. Confirmation of such measurably lateralised cognitive-motor interference in such a ubiquitous activity would be surprising and a potentially useful tool for the study of human motor control in health and disease.

If performing the Stroop task while walking is indeed associated with differential responses in the left and right arms, deliberate modulation of arm swing asymmetry in this way may provide information on the roles of cortical, subcortical and spinal networks in the control of locomotor arm movements. Attributes of the hitherto elusive human CPG may be studied by, for instance, assessing the phase dependent characteristics of spinal reflexes[146] with and without the Stroop task or assessing the magnitude of the Stroop effect on arm swing in patients with spinal or brain lesions.[108,139,148]

We aimed to build on the suggestive findings of Plate et al. by confirming the presence of a lateralised effect of the Stroop task on arm swing in a large cohort of healthy individuals and establishing whether left or right swing amplitudes are affected. We utilise a modified version of the traditional Stroop task[58] using a pseudorandomised presentation frequency, designed to eliminate any entrainment of rhythmic gait parameters and encourage constant attention.

As aging is associated with both a deterioration in both motor and cognitive control, we expected the Stroop effect on arm swing to be greatest in older adults.[56,60] We were also interested in establishing whether this effect was dose-dependent by assessing arm swing during two Stroop tasks with different degrees of difficulty. We shed light on potential mechanisms for this effect by assessing whether cognitive loading exerts its effect during arm protraction, retraction or both. Finally, we examine whether factors such as gender confer susceptibility to the Stroop effect.

2.3 Materials and methods

This two-centre study was approved by the Zurich cantonal ethics committee (KEK-2014-0004) and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. Healthy volunteers aged 18-80 and blinded to the purpose of the study were recruited locally via flyers and a website and gave informed, written consent. Volunteers were paid 25 Swiss Francs (approx. 25.50 USD) per hour for their time and excluded if any abnormalities were present on medical screening, including colour-blindness. Participants were recruited into three age groups; 18-39, 40-59 and 60-80, with recruitment stopped once 20 males and 20 females were included in each group (21 females were ultimately included in the younger age group). All participants completed a laterality index questionnaire assessing indicators including preference for hand and foot use.[149] Included subjects underwent a 40-minute acclimatisation protocol including four, 45-second rehearsals of the dual-task conditions on the treadmill. The rest of the acclimatisation period was spent practising treadmill walking tasks related to other studies.

Participants returned 1-7 days later for gait analysis. The timed 25-foot walk (T25FW)[43] and the 10-metre walk test (10MWT)[42] were performed twice. Both tasks were performed simultaneously at maximum gait speed from a standing start in a hallway marked with both distances. The maximal overground speed (OG_{max}) calculated from the mean of the two T25FW attempts. Treadmill speed was set at 50% OG_{max} for all trials. Three-dimensional gait analysis (Vicon, UK) was conducted while walking on an instrumented treadmill (120Hz, FDM-T, Zebris Medical GmbH, Germany) at one of two clinical gait laboratories. Data were recorded at 200Hz using Nexus 1.8.5 (Vicon) motion capture software. A reflective marker constellation was applied based on the Plug-in-Gait (Vicon) model[150] for the upper body and a modified Cleveland (Motion Analysis Corp., Santa Rosa, CA, USA) model for the pelvis and lower limbs.[106]

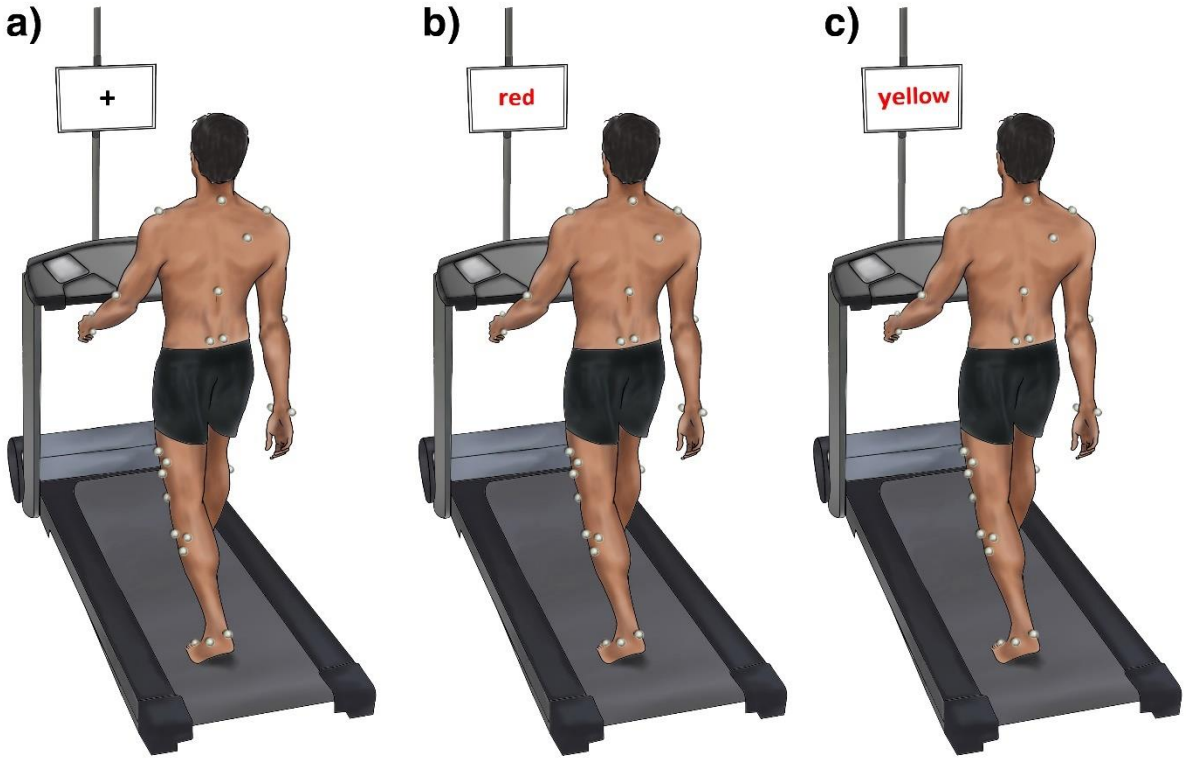


Figure 2.1. Experimental setup. For the normal walking condition (a), subjects walked on an instrumented treadmill while fixating a black cross. They then performed two Stroop colour-naming task (see methods) of differing difficulty. Image (b) shows the simpler task in which word and colour stimuli are congruent. In the more difficult, incongruent task (c) word and colour are discordant.

Subjects walked barefoot without handrail support. Stable gait was recorded over 30-45 seconds. For the normal walking condition (NW), participants were asked to walk while fixating on a cross displayed on a 22" LCD-monitor positioned 50 cm in front of the treadmill with its centre at eye height.

Cognitive distraction was achieved using a modified Stroop paradigm.[57,58] The presentations used are available at http://dx.doi.org/10.5061/dryad.2kd0b as supplementary material. The cross was replaced with text spelling out one of four colours (red, green, yellow and blue) presented at pseudorandom intervals using Powerpoint 2010 (Microsoft Corp., Redmond, WA, USA). The duration of each stimulus was between 600 and 1400ms. To avoid potential entrainment of temporal gait parameters and to encourage constant attention, stimulus duration was adjusted so that no more than two sequential stimuli had a duration within 200ms of that of the previous stimulus, although mean stimulus frequency was maintained at 1Hz over the trial. Two Stroop dual-task conditions were presented in the participant's self-declared native language and script (Figure 2.1). In the congruent Stroop task ($Stroop_{easy}$), the colouring of the text was consistent with that of the colour spelled out. In the incongruent task ($Stroop_{hard}$), all stimuli consisted of spelled-out colours presented in a discordant colour. Incongruent colouring was randomly assigned with the additional requirement that no two sequential stimuli were of the same colour. Participants were told to read the word silently to themselves while verbally stating the colour and to continue immediately with the next stimulus should they fall behind with their responses. Trial order was fixed with NW followed by $Stroop_{easy}$ and $Stroop_{hard}$. The number of errors made during the Stroop task were recorded for each trial.

Data were reconstructed, labelled, filtered and modelled in Nexus. Lower body gait cycle events were set using treadmill force-plate data. Arm swing cycle was defined by maximal protraction and retraction of the modelled wrist joint centre (WJC) - a virtual point half-way between the two wrist markers - relative to the pelvis in the progression axis. ProCalc 1.1 (Vicon) was used to output spatiotemporal gait parameters.

The three-dimensional trajectory (in mean distance travelled per gait cycle) of the WJC was taken as the principal measure of arm swing behaviour.[139] This was used as the basis of a

lateralised ASI (see formula in Section 2.2) [138,151] in which *L* is WJC trajectory on the left and *R* that on the right, giving a value between -100 and 100, with 0 representing perfectly symmetrical movements. Trials in which WJC trajectory was longer on the left yield a positive index, and vice versa.

ASI during normal treadmill walking varies considerably between individuals and this motivated our decision to exclude a priori from our analysis those with marked baseline asymmetry, with the rationale that any dual-task response may be masked by a ceiling effect if individuals exhibiting highly asymmetrical arm swing during NW were included. Based on observations in a pilot cohort,[108] we therefore excluded subjects exhibiting significant asymmetry to either the left or the right during NW, defined as an ASI of <-20 or >20.

Secondary outcome measures included the modelled sagittal shoulder angle cycle maxima and minima for the right and left upper limb to describe the contribution of sagittal extension and anteversion to any changes in ASI. These angles are relative to the trunk segment and are therefore theoretically unaffected by postural changes.[150] In the lower limb, we report step length, toe height at mid-swing and phase dispersion – a sensitive measure of interlimb coordination in which the timing of a given event is expressed as a percentage of the contralateral gait cycle[152,153] – for all limb pairs. In order to exclude anatomical differences in upper limb lengths as a confounding factor, left and right arm length was also calculated from the static calibration trial and an arm length symmetry index calculated.

Statistical analysis was performed using SPSS 23.0 (IBM Corp, Armonk NY, USA) and graphs produced using Prism 7.1.0 (Graphpad Software, La Jolla CA, USA). Gait parameters for each age group were analysed with a linear mixed model (LMM) in which condition (NW, $Stroop_{easy}$, $Stroop_{hard}$) was a repeated measure. Fixed effects comprised weight, height, gender, LI and walking speed. For significant effects, pairwise t-tests were performed across conditions with Bonferroni correction. Differences in demographic factors between groups were likewise assessed using a LMM without the condition factor. Correlations between ASI and Stroop performance were analysed using one-tailed Spearman's rho after grouping all trials into three groups; no errors, 1-5 errors or more than 5 errors. An explorative, post-hoc analysis of the

effect of gender on ASI changes was performed using the same LMM approach. The relationship between laterality index and change in ASI between NW and $Stroop_{hard}$ was assessed with Pearson's correlation coefficient. Statistical significance was set at $p \leq 0.05$ for all tests.

2.4 Results

Of 145 volunteers, 24 were excluded at medical screening. Data were unusable for two subjects who stumbled during some trials. A further 36 exhibited marked baseline arm swing asymmetry and were excluded; eight with right-dominant and 28 with left-dominant arm swing (Supplementary Figure 2.1). Distribution of handedness and arm length symmetry was similar in both excluded groups and the main, included cohort. Mean baseline ASI for the whole cohort prior to the exclusion of these participants was 6.16±1.75 (i.e. trajectories were approximately 6.6% longer on the left). More details of the full cohort including excluded participants are available in Supplementary Figures 2.1 & 2.2.

Age Group	n	Age (years)	Percent female	Weight (kg)	Height (cm)	Percent right-handers	Walking speed (km/h; median ± IQR)	25FWT (s)	10MWT (s)	6MWT (m)	Arm length asymmetry index (L dominance is positive)
18 – 39	31	28.6±4.9	51.6	71.3±15.5	173±9	93.5	4.3±0.9	3.28±0.44	4.30±0.61	726±80	-0.58±2.18
40 – 59	23	47.5±6.1	52.0	73.5±13.0	172±8	96.0	4.0±0.6	3.50±0.47	4.62±0.63	701±83	-0.66±1.89
60 – 80	29	67.8±4.5	62.1	65.5±10.0	168±9	96.6	3.7±0.6	3.76±0.60	4.91±0.82	671±100	-0.26±2.35

Table 2.1 Subject characteristics. Characteristics of the included participants, separated into age groups. All data presented as means with standard deviation except where indicated. IQR; interquartile range, T25FW; timed 25-foot walk, 10MWT; 10-metre walk test, 6MWT; 6-minute walk test.

Eighty-three subjects were therefore included in the final analysis; 31 aged 18-39, 23 aged 40-59 and 29 aged 60-80. Group characteristics are summarised in Table 2.1. Gender distribution was similar across age groups. Performance in walking tests declined with age, with longer times in both the timed T25FW ($p = 0.008$) and 10MWT ($p = 0.013$) in the 60-80 age group. As treadmill speed was determined by the 25FWT result, median walking speed was 4.3, 4.0 and 3.7kmh-1 in the younger, middle-aged and older groups respectively (younger and older significantly different; $p = 0.005$). Discrepancies in arm length (left vs right) were negligible in all groups.

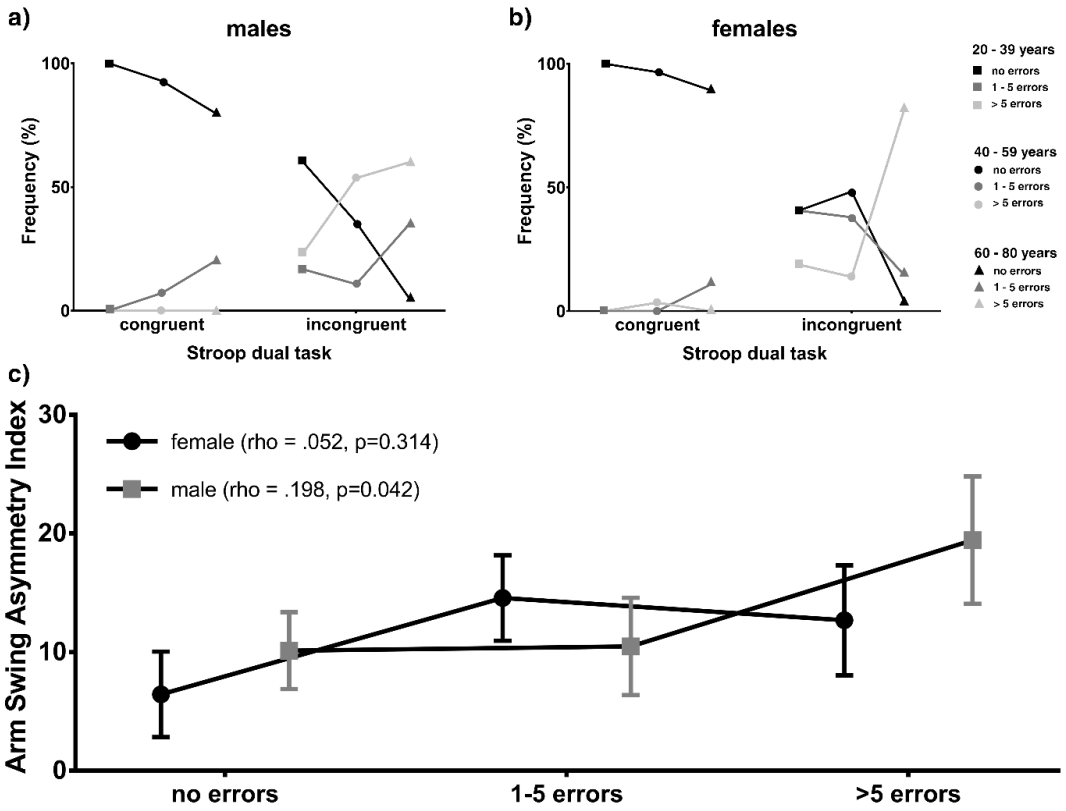


Figure 2.2. Performance in congruent and incongruent Stroop tasks. a) males, b) females. Relative frequency of Stroop trial error rate trichotomised into no errors, 1-5 errors or >5 errors. c) Correlation (Spearman's rho) between arm swing asymmetry index and error rate during the incongruent Stroop task.

Performance in both the congruent and incongruent Stroop tasks became worse with age (Figure 2.2a, b). Errors were rare in the congruent task, with no 20-39 year olds making more than five mistakes. Males made more mistakes than their female counterparts in the congruent task. In the two younger age groups, men were more likely to make more than five errors during the incongruent task than women, but women's performance deteriorated significantly over 60 years of age during this task, in which 89.3% of older females and 80% of older males made more than 5 errors.

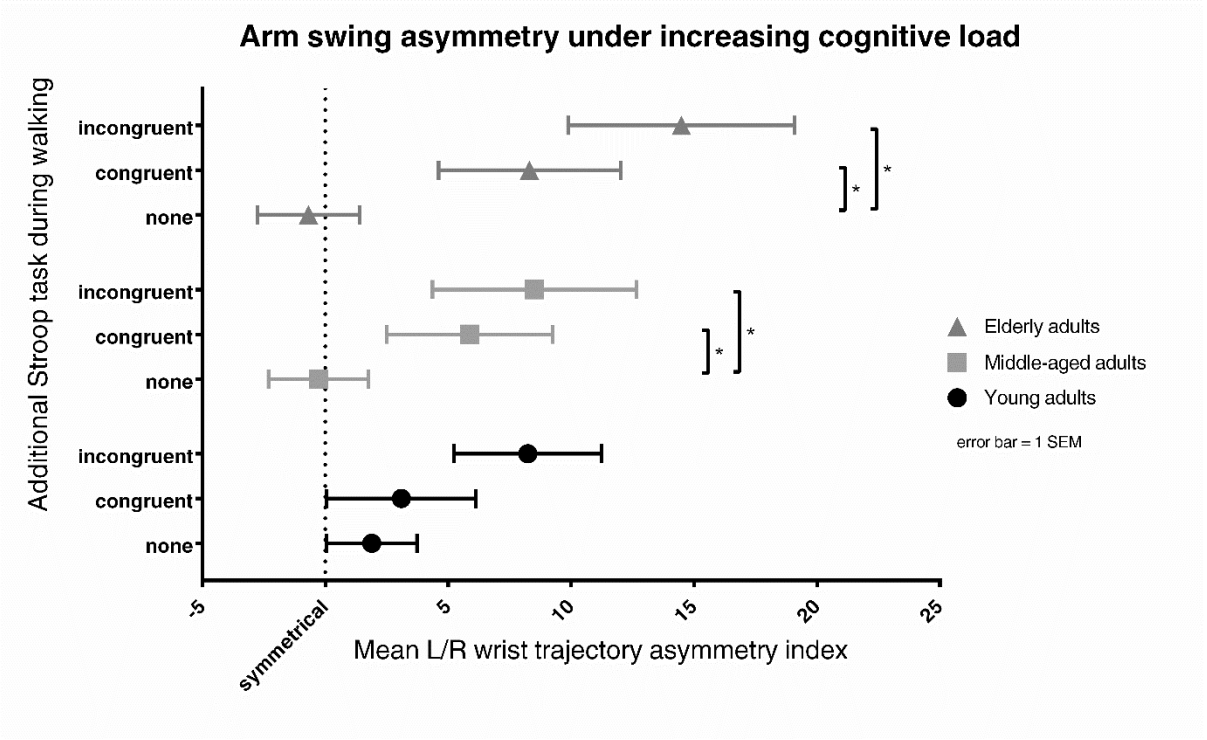


Figure 2.3. Arm swing asymmetry under increasing cognitive load. Wrist trajectory asymmetry index is calculated using the left and right 3D wrist centre trajectories, with left dominance resulting in a positive value and vice versa. ASI is given as the mean value per gait cycle over a trial of 45 seconds (approximately 42 gait cycles at 4kmh-1). SEM; standard error of the mean. Statistical significance was determined using a linear mixed model with post-hoc t-tests. P values are corrected for multiple pairwise within-age group comparisons using the Bonferroni method.

Overall, ASI increased under cognitive load, from (mean±SEM) 0.37±1.13 to 5.69±1.94 in $Stroop_{easy}$ and again to 10.49±2.27 in $Stroop_{hard}$. This represents left WJC trajectories respectively 0.4%, 6.0% and 11.7% larger than those on the right. All groups demonstrated the same tendency, with mean ASI increasing from 1.89±1.83 to 3.10±3.03 and 8.24±3.01 in the 18-39 age group, -0.28±2.03 to 5.87±3.38 and 9.19±3.31 in the 40-59 age group and -0.68±2.07 to 8.31±3.70 and 15.16±3.80 in the 60-80 age group (Figure 2.3). These increases in ASI between normal walking (NW) and $Stroop_{easy}$ were significant for middle-aged ($p = 0.048$) and older adults ($p = 0.009$), as were those between NW and $Stroop_{hard}$ in the middle-aged ($p = 0.009$) and older ($p < 0.000$) groups. Overall, ASI did not correlate with Stroop performance (rho .114, p=0.071) but there was a moderate correlation in males (rho .198, p=0.042; Figure 2.2c).

Changes in asymmetry were driven by reductions in right wrist joint centre (WJC) trajectory relative to those on the left (Figure 2.4). This reduction in mean right arm swing relative to baseline was significant in the older age group, in which right trajectory length decreased by 13.1% ($p = 0.049$) and 22.1% ($p < 0.000$) during $Stroop_{easy}$ and $Stroop_{hard}$ conditions respectively, with the reduction between the dual-tasks also significant ($p = 0.035$).

Sagittal shoulder and elbow angles were analysed to determine whether arm swing amplitude changes were occurring during arm protraction, retraction or both (Figure 2.5a). In older adults, maximal shoulder anteversion decreased (mean±SD; NW: 4.35±10.07°, $Stroop_{easy}$: 1.21±10.35°, $Stroop_{hard}$: -0.54±11.62°; $p \leq 0.032$) under both conditions, while right maximal elbow flexion also reduced between the NW and $Stroop_{hard}$ conditions (Figure 2.5b; NW: 53.69±11.49°, $Stroop_{hard}$: 48.34±8.08°; $p = 0.012$). A significant effect was seen neither during flexion on the left, nor in extension bilaterally. In the two younger age groups, trends towards decreases in right shoulder and elbow flexion did not reach significance (data not shown). In the younger age group in whom a non-significant increase in left WJC trajectory was seen (Fig. 4), this was manifested as a trend towards increases in both extension and flexion maxima.

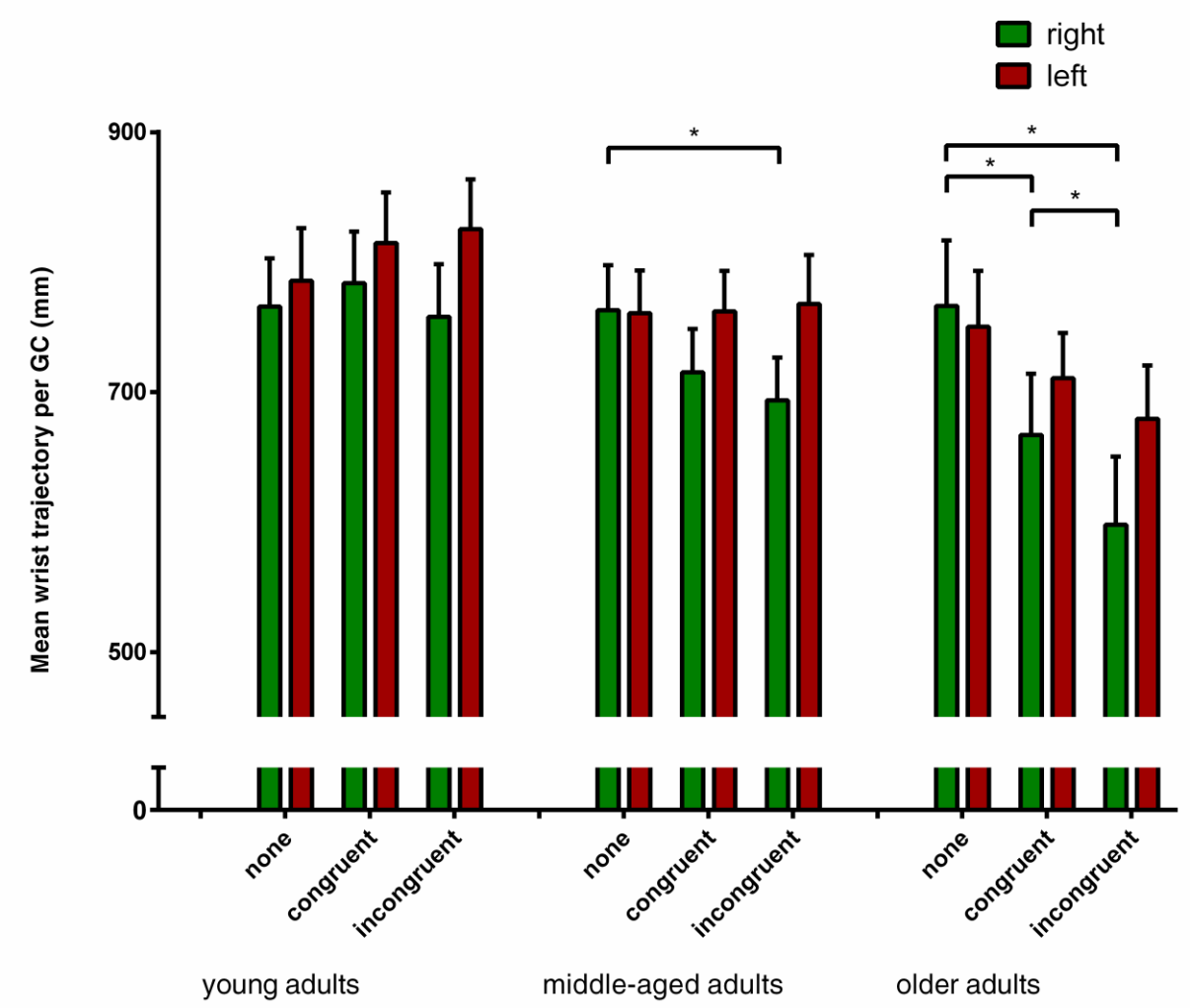


Figure 2.4. Absolute wrist trajectory length. Three-dimensional wrist joint centre trajectories for younger, middle-aged and older adults during normal walking and during a congruent and an incongruent Stroop dual-task. GC; gait cycle. Error bars indicate 1 standard error of the mean. Statistical significance was determined using a linear mixed model with post-hoc t-tests. P values are corrected for multiple pairwise within-age group comparisons using the Bonferroni method.

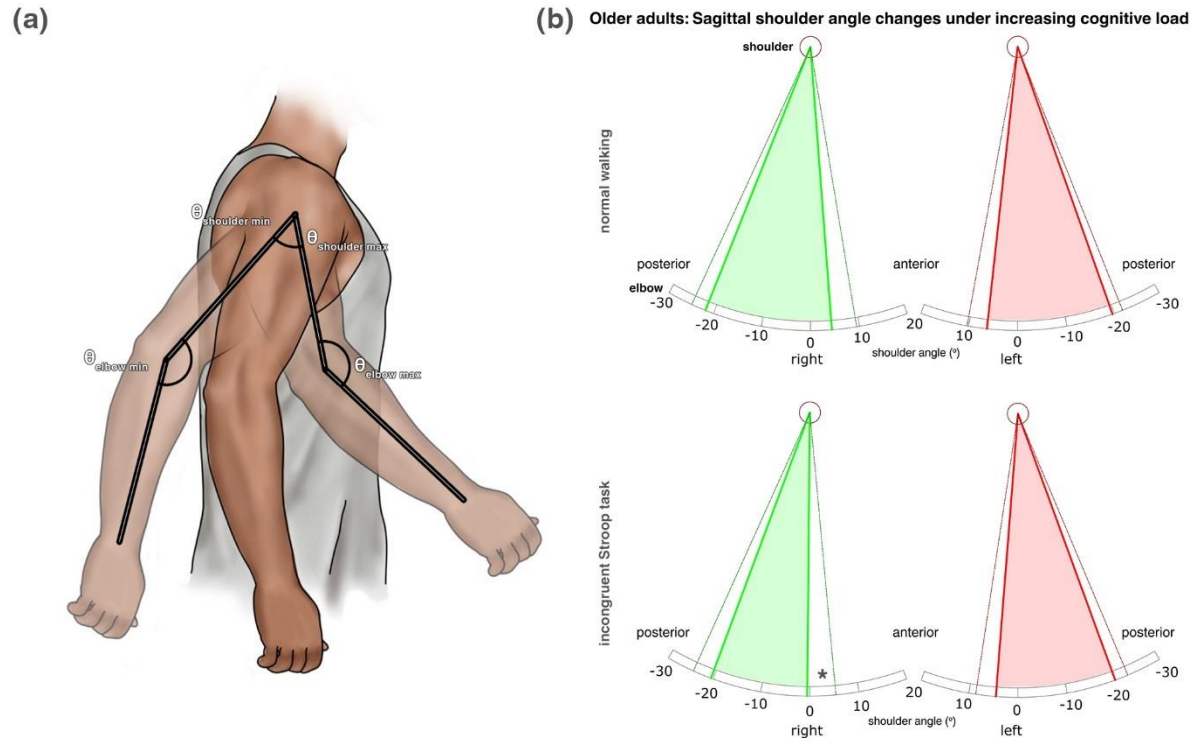


Figure 2.5. a). Sagittal gait cycle mean joint angle maxima and minima based on the approach used by Roggendorf et al. [6] b) Sagittal shoulder angle changes during normal walking and under increased cognitive load (incongruent Stroop task) in older adults walking on a treadmill. Diagrams represent the right (green) and left (red) mean sagittal shoulder angle maxima and minima (thick lines) per gait cycle with associated single standard deviations (thin, dark lines). A significant decrease in shoulder flexion in the incongruent Stroop task is indicated by *. Elbow flexion was also reduced under increased cognitive load, with preserved extension (not shown; see results section).

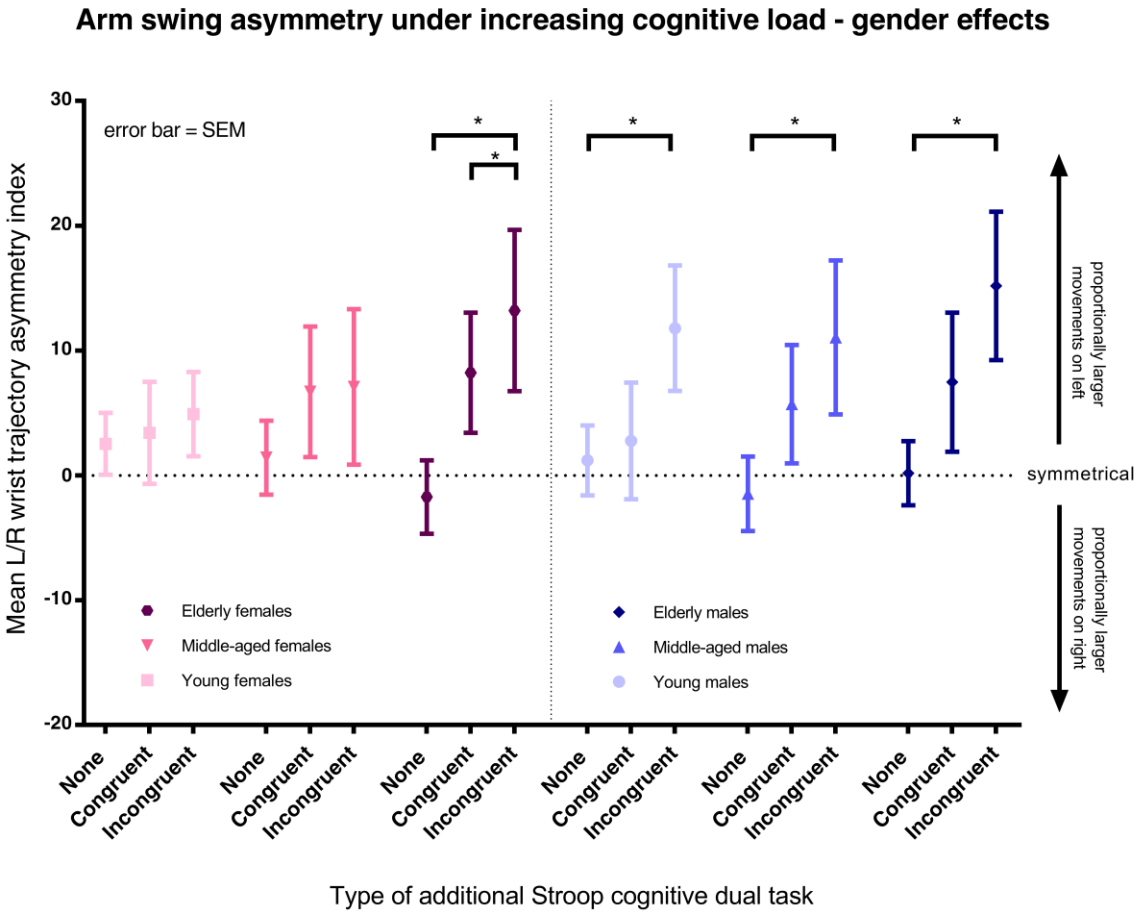


Figure 2.6. Arm swing asymmetry under increasing cognitive load – gender effects. Wrist trajectory asymmetry index is calculated using the left and right 3D wrist centre trajectories, with left dominance resulting in a positive value and vice versa. ASI is given as the mean value per gait cycle over a trial of 45 seconds (approximately 42 gait cycles at 4kmh-1). SEM; standard error of the mean. Statistical significance was determined using a linear mixed model with post-hoc t-tests. P values are corrected for pairwise within-group comparisons using the Bonferroni method.

While, in the older age group, both genders responded similarly to the addition of the Stroop task with increases in ASI (males; NW: 0.17±2.57, $Stroop_{easy}$: 7.47±5.58; p = ns, $Stroop_{hard}$: 15.19±5.95; p = 0.09, females; NW: -1.73±2.94, $Stroop_{easy}$: 8.23±4.82; p = 0.021, $Stroop_{hard}$: 13.21±6.46; p = 0.003), gender differences were observed in the two younger age groups (Figure 2.6). Males aged 18-39 showed a significant increase in ASI relative to NW during $Stroop_{hard}$ (1.20±2.80 to 11.79±5.03; p = 0.047). Similarly, males aged 40-59 exhibited significant leftward shifts in ASI from -1.47±2.98 to 5.71±4.75 in $Stroop_{easy}$ (p = 0.044) and 11.05±6.17 in $Stroop_{hard}$ (p = 0.010). Females in both younger groups showed no significant changes in ASI.

The cohort included only four left-handers, including two educated as right-handers. Mean(±SD) laterality index (-13 = fully left lateralised, 13 = fully right) was 8.5±4.0. There was no correlation between laterality index (neither the full index nor its motor subcomponents) and changes in ASI under increased cognitive load.

Changes in lower body spatiotemporal parameters are summarised in Supplementary Table 2.1 and Supplementary Figure 2.3. Gait in older adults during $Stroop_{hard}$ was characterised by increased stride-to-stride step length variability and small but significant reductions in foot clearance bilaterally. Stride time and stride time variability was unaffected by condition or age group. Measures of interlimb temporal coordination remained unchanged across conditions (Supplementary Figure 2.4).

2.5 Discussion

As expected, our cohort broadly replicates findings relating to the effect of the Stroop and other cognitive dual-tasks on lower body kinematics,[53,63,98] with healthy older subjects exhibiting a marked increase in step length variability and decreased foot clearance under increased cognitive load (Supplementary Table 2.1, Supplementary figures 2.3 & 2.4). We contribute the novel finding that increasing cognitive loading in a language task during treadmill walking results

in a corresponding, dose-dependent increase in left-lateralised arm swing. This effect is age- and sex-dependent, with men of all ages susceptible to enhanced asymmetry under cognitive load, while women under the age of 60 are resistant. The asymmetry shift is driven by an attenuation of right arm swing amplitudes and, at least in older adults, by reduced flexion at the right shoulder and elbow during limb protraction.

Recent work reported the surprising finding that ASI is modulated through both the Stroop task and a serial sevens counting paradigm in 60 healthy adults.[138] The authors noted a left-dominant arm swing asymmetry, significantly stronger in the Stroop task than during serial subtraction, and speculated that the additional left hemispheric language processing of the former underlay this difference. Whether reductions in right or increases in left swing magnitude were responsible for this shift was not stated. The data presented here clearly confirm that such asymmetry, provoked by the Stroop task, is indeed directional and is driven by a significant decrease in arm swing amplitude on the right. We also show that the degree of right arm swing attenuation is modulated by task difficulty, age and gender, with those aged 60 and above consistently showing the largest shifts in ASI in $Stroop_{hard}$. Supraspinal processing thus indeed appears to result in a dose-dependent paucity of right arm swing during walking.

Suppression of arm flexors

The Stroop task may result in reduced left supraspinal drive acting upon the right cervical part of the locomotor pattern generator underlying arm swing, with candidate sites of upstream interference the left frontal regions and basal ganglia circuits common to both the control of locomotor behaviour and cognitive control.[61,62,140,141,143,144,154,155] It has been proposed that arm movements are regulated by task-dependent neuronal coupling,[135,156,157] through which the rhythmic activation of cervical CPG networks is facilitated during locomotion and inhibited when goal-directed upper limb control is desired.[145,158] Such unilateral gating allows locomotor movements to continue in one arm while the other is engaged in a skilled motor task (e.g. while gesticulating or manipulating an object). The predominantly verbal Stroop dual-task may thus lead, through predominant activation of left cortical and basal ganglia structures,[141,159] to

suppression of rhythmic locomotor activity in the right arm via a non-specific decrease in supraspinal drive.

Alternatively, and in keeping with some evidence that Stroop performance causes interference in both hemispheres,[62,144] dual-task processing may lead to cortically-mediated, decreased drive to spinal centres, the effects of which only manifest in the dominant arm. This interpretation is supported by the existence of an apparent tendency towards asymmetrical, left-dominant arm swing during normal treadmill walking (i.e. without a dual-task) in this and previous reports.[108,138,151,160] This puzzling baseline asymmetry may result from the attentional demands associated with walking in unhabituated conditions,[161,162] although our participants underwent lengthy treadmill acclimatisation. There was an insufficient number of left-handers in our sample to test this hypothesis, but others have demonstrated that directional arm swing asymmetry is not related to handedness during normal treadmill walking[138,151] and there was no correlation between ASI changes and LI in our overwhelmingly right-handed cohort. Why dominant arm swing amplitude should be more sensitive to decreased bihemispheric supraspinal drive is not clear. Further research, considering the full complexity of human handedness and its interplay with cognition (e.g. left-handedness with preserved *vs* reversed hemispheric language specialisation), would be of value.

Interestingly, asymmetry in the older adults, the group most affected by the Stroop task, was driven by a reduction in shoulder and elbow flexion and may be reflective of a unilateral unmasking of an extensor-dominant GPG[163] as cortical drive is reallocated away from locomotion. In the legs, a dissociation exists between more centrally modulated flexor activity and extensors under the control of more autonomous, proprioceptive pathways.[164] An analogous situation may exist in the arms, where differential corticospinal projection to biceps and triceps mirrors that in the tibialis anterior and soleus muscles[114,165] More convincingly, this flexor / extensor dissociation may arise from reduced, corticospinally-modulated biceps activity in the context of unimpaired extension under the control of the reticulospinal tract.

Facilitation of arm extensors

An alternative explanation assumes that, rather than decreasing supraspinal drive, engaging in the Stroop task augments cortical inputs to the contralateral upper limb compared to NW. While both proximal flexors and extensors are active during arm swing, it is believed that forward swing is more passive than retraction and that eccentric extensor activation is used to arrest arm protraction prior to swing reversal.[135,166] Inhibitory transcranial magnetic stimulation reduces EMG activity in the posterior deltoid during arm swing[37], so it follows that facilitation would result in reduced shoulder anteversion under cognitive load. Ascertaining the effect of the Stroop task on upper limb EMG would be illuminating.

Arm swing asymmetry in PD patients is, in contrast to the reduction in flexion seen here, characterised by deficits in shoulder *extension*.[139,148] Asymmetry in PD may therefore be due to an entirely different, pathological mechanism such as rigidity. Establishing the relative contributions of flexion and extension to ASI in PD may prove an improved diagnostic criterion, as, while (absolute) ASI appears to be a sensitive indicator of early PD,[139] its specificity is hampered by high variability in healthy controls.

Gender

A gender sub-analysis showed that the effect of aging on ASI shift was specific to females (Fig. 3). This unexpected and pronounced resistance to right arm swing attenuation in pre-menopausal women may be due to oestrogen-mediated plasticity and attendant redundancy in the prefrontal cortex (PFC), where oestrogen receptors are plentiful[167] and oestradiol increases dendritic spine density in primates.[168] In women, there is an oestrogen-related enhancement of cognitive control and inhibition of inappropriate responses[169,170] while susceptibility to the Stroop task is ameliorated by oestrogen treatment after the menopause.[171] The left PFC – widely implicated in cognitive control[172] and activated during active stepping,[64] treadmill walking[173] and the Stroop task[61,174] – is thus a strong candidate for the site of the cognitive-motor interference underlying the observed ASI shifts in men and older women. Targeting of the left PFC with

oestrogen therapy or transcranial magnetic stimulation[175] may improve motor control in elderly fallers and patients with gait instability.

It is noteworthy that the increase in ASI observed in young males (Fig. 5) is, in contrast to those in the older age groups, driven by an absolute increase in left arm swing, with a relatively smaller reduction on the right (Fig. 3). While females in this group slightly increase their arm swing bilaterally, males failed to do so on the right, accounting for their increased, left-dominant asymmetry.

Interlimb coordination

Interlimb coordination was highly preserved irrespective of age or gender and despite the significant changes in the spatial characteristics of arm movements under increased cognitive load. That the timing of key temporal elements of arm swing is not affected by cognitive load is in keeping with a predominantly spinal source of interlimb coordination along propriospinal connections between the cervical and lumbar CPG elements.[145,156,176,177]

Methodological considerations

The dual-task methodology presented here differs slightly from that of previous researchers[138] and may account for the strength of the results. Presenting rhythmic stimuli risks stimulus-motor entrainment,[109,127] so we chose to present Stroop cues at irregular intervals around a mean frequency of 1Hz (range 600-1400ms). This had the additional, beneficial effect of making the Stroop task harder and requires constant, rather than intermittent, attention as subjects could not anticipate stimulus duration.

Walking speed was set as 50% of OG_{max}, approximating preferred speed, at which arm swing is well established and in phase with the legs. This resulted in different median speeds in the three age groups. However, while arm swing amplitude varies as a function of gait speed, ASI does not.[138] In practice, the difference in median speeds was small and mean amplitudes were similar during NW in all three groups (Figure 2.4).

Exclusion criteria

Determining an appropriate cut-off value for exclusion in experiments measuring ASI is difficult for a number of reasons, especially as a degree of left-dominant asymmetry appears to be physiological during normal treadmill walking.[108,138,151,160] The approaches taken by different research groups to calculate ASI are diverse, with various two-dimensional sagittal metrics most commonly used in conjunction with two competing calculations; the ASI and asymmetry angle[178,179]. Furthermore, an absolute, non-directional ASI is used by many authors whose hypotheses do not investigate laterality. Unfortunately, the only study using comparable, three-dimensional trajectories to describe asymmetry[139] is of limited usefulness in informing cut-off values in our cohort as it featured overground walking and used an absolute asymmetry angle. We therefore referred to data from a previous study in our laboratory[108], in which three of 12 healthy control subjects who exhibited normal walking ASI values of +20 or more showed evidence of a ceiling effect under cognitive loading, to set inclusion baseline ASI values of -20 to +20.

This approach proved justified as no consistent dual-task effect was observed amongst the 28 subjects excluded for baseline ASI values over 20 (Supplementary Figure 2.1). Individual responses were highly variable (Supplementary Figure 2.2). Only 36% of individuals in this group showed an ASI shift between NW and $Stroop_{hard}$ of > 10, compared to 46% of those in the included group (Supplementary Figure 2.2). This fact, and the observation that variance was 13% smaller in the group with ASI over 20 compared to the included group, suggest that a ceiling effect indeed contributed to the findings observed in this group. The eight individuals with strongly right-dominant asymmetry during NW (< -20) showed no common response to cognitive load (Supplementary Figures 2.1 & 2.2).

Some healthy individuals may exhibit marked baseline asymmetry due to acquired atypical gait patterns[180] and the possibility exists that some baseline asymmetry may have been a subclinical manifestation of neurological or musculoskeletal disease in our participants. Both causes of asymmetry may result in different responses to cognitive load.

Outlook: Right hemisphere dual-tasks

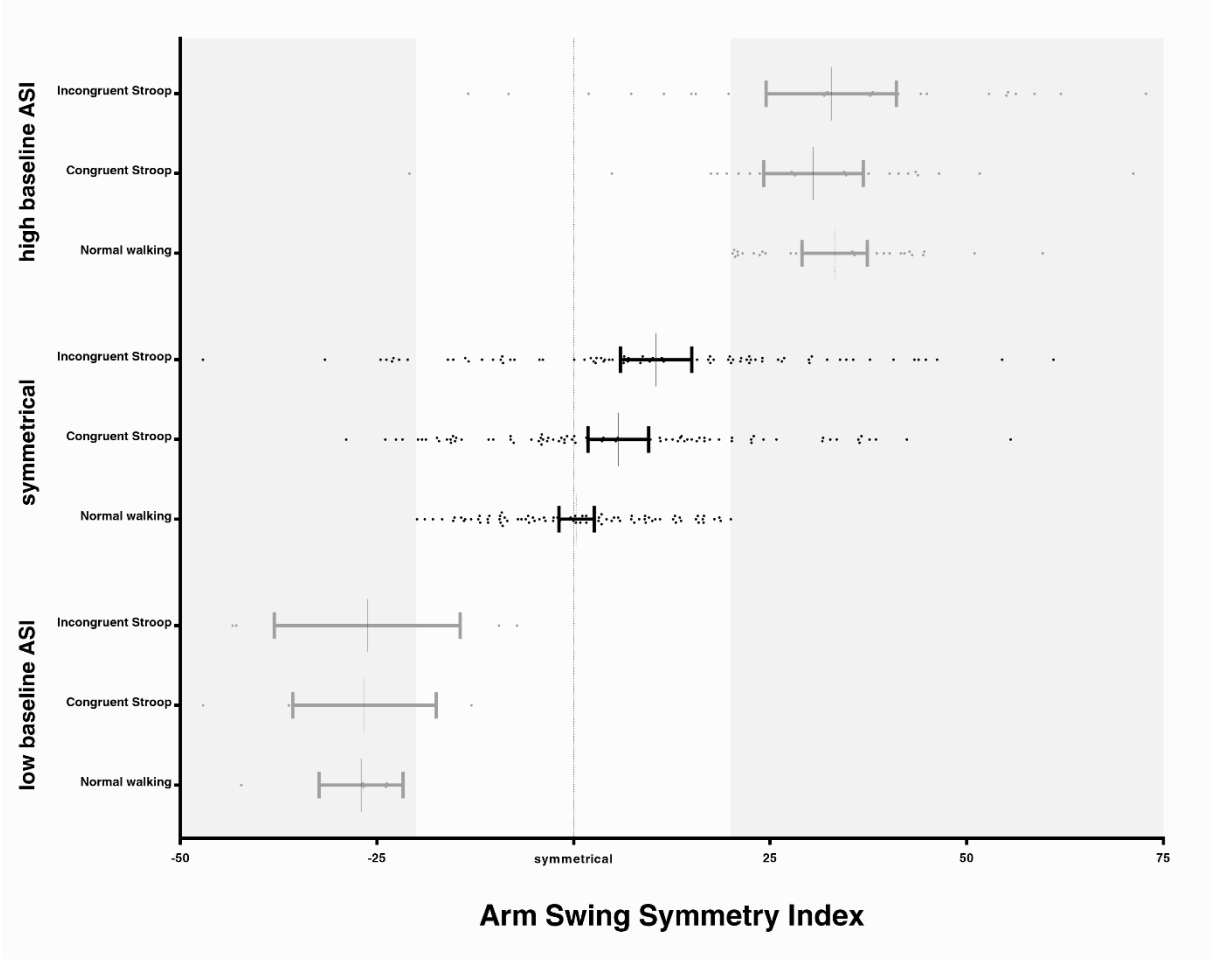
It would be interesting to apply this approach with a task subsisting on primarily right hemisphere structures, with the expectation that reciprocal effects on left arm swing may be observed. To this end, our group has performed pilot experiments with an increasingly difficult bisecting lines task (Landmark task)[181] in individuals known to be susceptible to the ASI Stroop effect, with negative results. However, this task does not recruit right prefrontal networks[182] so future experiments with an appropriate paradigm may be more successful.

2.6 Conclusions

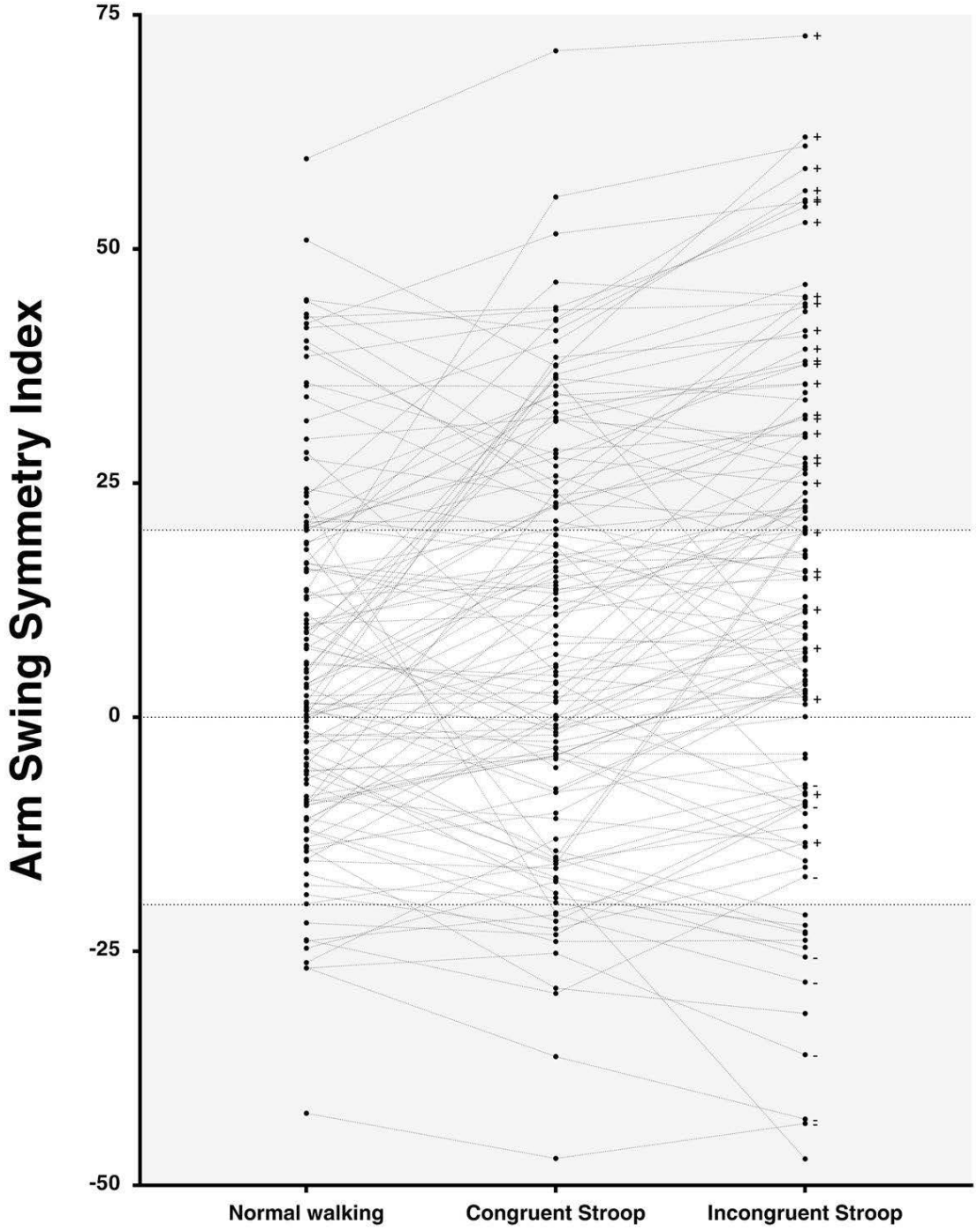
Reduction in right arm swing appears to be the norm in humans performing a motor-cognitive dual-task, confirming a prominent role of the brain in arm swing behaviour. In older adults, asymmetry is characterised by reduced arm protraction, suggesting that upper limb flexors are under more direct supraspinal control and susceptible to interference. Alternatively, the Stroop task may enhance cortical drive to the right arm extensors, braking passive shoulder anteversion through enhanced eccentric extensor contraction. Overcoming this interference appears to be a trait unique to younger females and implies significant gender differences at the top of the hierarchical chain of locomotor control. Applying this paradigm to patients with PD, subcortical stroke and SCI may permit further insights into the control of arm movements in human locomotion.

		Step length		Step width		Phase dispersion					Foot clearance	
	Additional Stroop task	Mean (mm)	Variability (CoV; %)	Mean (mm)	Variability (CoV; %)	L arm to R arm (% of gait cycle)	L leg to R leg (% of gait cycle)	L arm to R leg (% of gait cycle)	R arm to L leg (% of gait cycle)	L leg to L leg (% of gait cycle)	Left toe height at midswing (mm)	Right toe height at midswing (mm)
Young adults (18 – 39 years)	None (baseline)	592.3±9.8	1.82±0.06	73.62±4.41	29.68±2.32	50.96±0.45	49.95±0.12	62.63±0.55	63.63±0.50	87.31±0.55	22.8±0.8	22.2±0.8
	Congruent	592.1±9.8	1.82±0.09	77.71±4.62	28.90±2.39	50.96±0.37	50.15±0.12	62.58±0.53	63.71±0.47	87.20±0.57	21.8±0.8	**21.2±0.8***
	Incongruent	588.0±9.4	1.89±0.10	78.82±4.97	26.78±2.15	51.10±0.36	50.12±0.11	62.79±0.50	64.00±0.44	87.09±0.52	22.1±0.8	21.3±0.8
Middle aged adults (40 – 59 years)	None (baseline)	563.4±9.2	1.94±0.11	76.24±6.55	29.35±5.05	51.58±0.31	49.98±0.15	63.24±0.53	65.76±0.68	86.78±0.54	23.9±1.2	25.8±1.6
	Congruent	575.4±10.3	**1.73±0.08***	80.37±7.04	26.17±2.94	51.41±0.35	49.90±0.14	63.20±0.57	65.02±0.58	86.89±0.54	**21.8±0.9***	**22.9±1.0***
	Incongruent	566.7±10.1	1.81±0.11	85.76±7.28	23.20±3.00	51.04±0.41	49.97±0.10	63.49±0.58	64.91±0.59	86.42±0.59	**21.3±0.8***	23.4±1.0
Older adults (60 – 80 years)	None (baseline)	536.9±11.7	2.45±0.12	73.32±5.59	31.11±2.38	52.10±0.55	50.05±0.12	65.47±0.67	66.68±0.88	84.50±0.65	22.1±1.0	22.2±1.1
	Congruent	**548.9±10.6***	2.35±0.13	74.87±5.39	33.49±4.16	51.32±0.67	50.09±0.15	65.64±0.76	66.12±0.84	84.27±0.76	**19.2±0.9***	**18.9±0.9***
	Incongruent	542.0±11.5	**2.99±0.24*†**	79.26±5.67	33.84±5.66	50.97±0.68	50.12±0.15	65.90±0.82	66.12±0.81	83.59±0.80	**19.3±0.9***	**19.1±0.9***

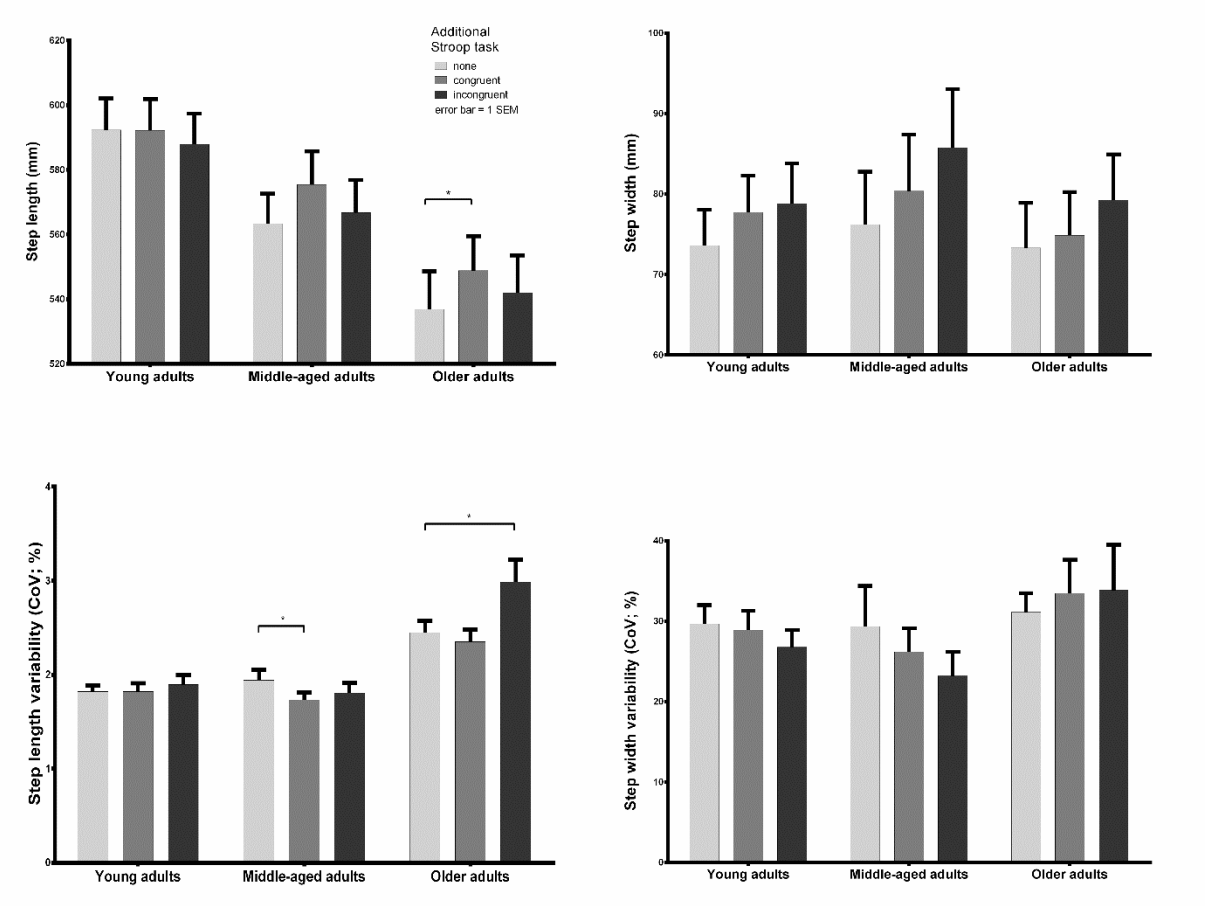
Supplementary Table 1.1 (previous page). Spatiotemporal gait parameters under increasing cognitive load. Mean ± SEM of gait parameters under three walking conditions on a treadmill; normal walking (no additional cognitive load), walking while performing a congruent Stroop task and walking while performing an incongruent Stroop task. Step length is the distance in the progression axis from heel strike to ipsilateral heel strike. Step width is the distance in the lateral axis from heel strike to contralateral heel strike. Phase dispersion is calculated as the point in the time normalised gait cycle at which the coordinated event occurs during the cycle of the second limb expressed as a percentage of the latter, with maximal arm protraction taken as the index event for arm swing and toe-off taken as that for stepping. Foot clearance is reported as the distance in the vertical axis of the toe marker from the treadmill at the point of ipsilateral mid swing. * indicates significant change to baseline walking condition, † indicates significant change between incongruent and congruent Stroop task condition (linear mixed model, $p \leq 0.05$). CoV; coefficient of variation.



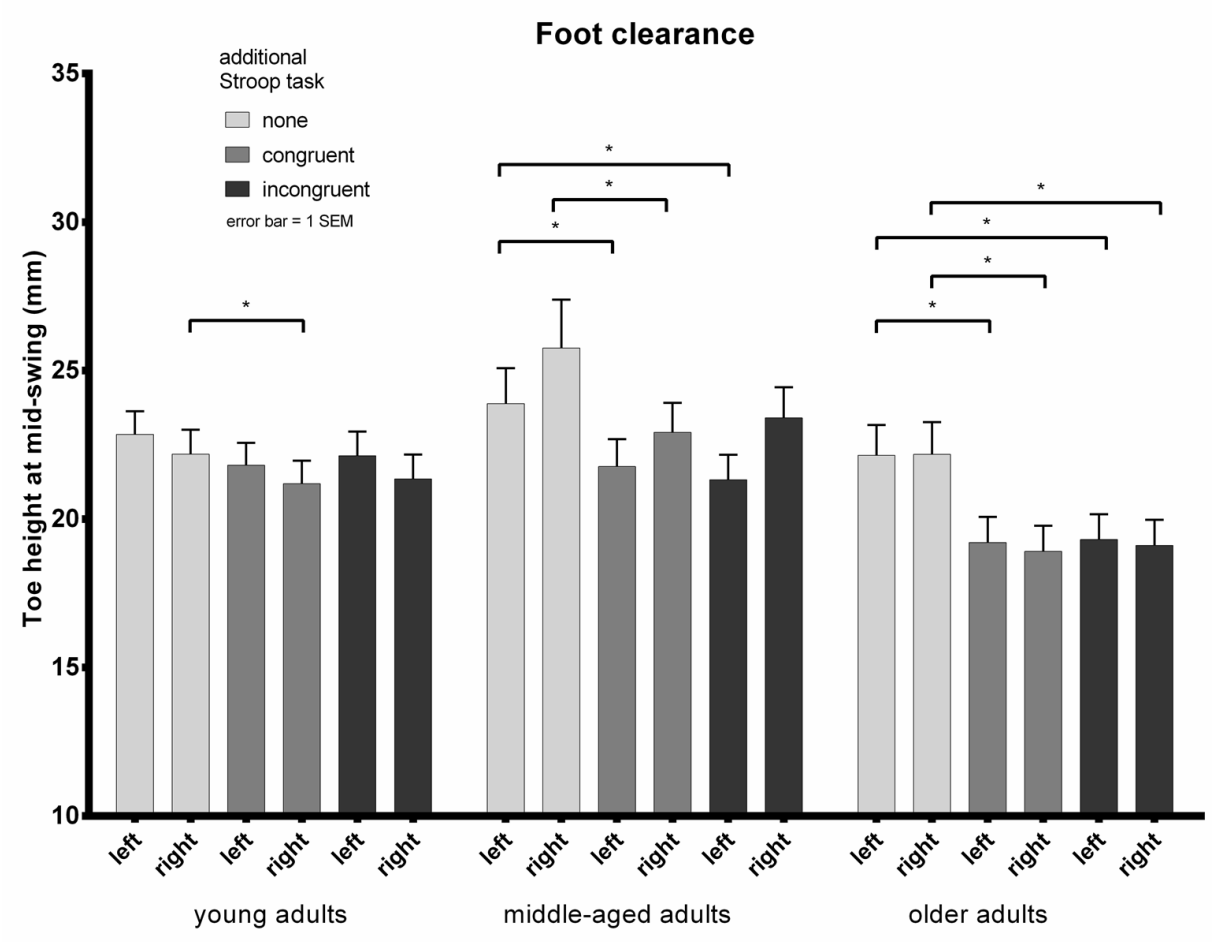
Supplementary Figure 2.1. Effect of cognitive load on ASI for the entire cohort (n = 119), separated into three groups based on inclusion status. Only individuals exhibiting an ASI between -20 and 20 were included in the final analysis. Low baseline ASI; excluded group exhibiting a right-dominant ASI during normal walking of < -20 (n=8). High baseline ASI; excluded group exhibiting a left-dominant ASI during normal walking of > 20 (n=28). ASI is given as the mean value per gait cycle over a trial of 45 seconds (approximately 42 gait cycles at 4kmh-1). Error bars represent 95% confidence intervals. ASI; arm swing symmetry index.



Supplementary Figure 2.2. Changes in ASI in individuals under increasing cognitive load for the entire cohort (n=119), including excluded groups. ASI is given as the mean value per gait cycle over a trial of 45 seconds (approximately 42 gait cycles at 4kmh-1). Individuals' ASI values in the three different trials are linked with a dotted line. Individuals with an ASI less than -20 andor more than 20 during normal walking were excluded from the final analysis. The ASI of these individuals during the incongruent Stroop task are indicated by a + (ASI during normal walking > 20) or a – (ASI during normal walking < -20).



Supplementary Figure 2.3 Basic spatiotemporal parameters under increasing cognitive loads during treadmill walking in younger, middle-aged and older adults. Statistical significance was determined using a linear mixed model with post-hoc t-tests. P values are corrected for multiple comparisons within each age group using the Bonferroni method. Error bars indicate 1 standard error of the mean. CoV; coefficient of variation.



Supplementary Figure 2.4. **Mean toe clearance at ipsilateral mid-swing under increasing cognitive load.** Statistical significance was determined using a linear mixed model with post-hoc t-tests. P values are corrected for multiple comparisons within each age group using the Bonferroni method. Error bars indicate 1 standard error of the mean.

Chapter 3: Modulating arm swing symmetry with cognitive load: a window on rhythmic spinal networks in humans?

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3.1 Abstract

In healthy subjects, changes in arm swing symmetry while walking are observed when a cognitive dual task is added, with a tendency towards left-dominant arm swing as cognitive load increases. We applied a modified Stroop word / colour discrimination paradigm to investigate this effect in spinal cord injured (SCI) patients. Six patients with cervical SCI (cSCI), six with thoracic injuries (tSCI; all 12 patients AIS D) and 12 healthy, matched controls underwent 3D gait analysis while walking normally at a comfortable speed (NW) and when performing an additional congruent (CS) and incongruent (IS) Stroop task. Arm swing asymmetry index (ASI) – in which positive values indicate proportionally more movement on the left and vice versa – was calculated. Even in the baseline NW condition, all three subject groups showed larger arm movements on the left. In controls, ASI increased (NW:13.7±6.3, CS:16.6±6.4, IS:19.6±7.8) as the task became more demanding. A larger shift in tSCI patients (NW:15.8±6.0, CS:23.4±3.8, IS:30.7±4.4) was driven by a significant reduction in right wrist trajectory ($p = 0.014$), while cSCI patients showed a small reduction in mean ASI with high variability (NW:14.2±10.7, CS:9.3±13.5, IS:6.0±12.9). The effect of the IS task on ASI compared to baseline (NW) was significantly different between tSCI (+12.5±6.3) and cSCI (-8.2±6.0) patients ($p = 0.011$). Disruption of the long propriospinal connections coordinating arm and leg movements during walking may explain the heightened sensitivity to manipulation of cognitive load in tSCI, while the more robust automaticity in cSCI may be due to impaired supraspinal inputs in the context of preserved intraspinal pathways.

3.2 Introduction

Asymmetry of the rhythmic upper limb movements during ambulation has been identified as a potentially useful diagnostic indicator of impaired motor control.[139,148] In healthy individuals, arm swing asymmetry has recently been observed to increase while engaging in cognitive dual task during walking.[137,138] This increase in asymmetry may be directional, with increasing cognitive load in the Stroop word/colour discrimination task causing asymmetry to shift towards proportionally smaller arm swing amplitudes on the right.[138] Why this effect should be lateralised in this way is not entirely clear, but its evaluation in SCI patients may present a useful method to investigate motor control of the upper limbs during ambulation.

The upper and lower limbs in human locomotion are thought to be coordinated via bidirectional propriospinal fibres coupling lumbar and cervical spinal locomotor circuits; networks capable of producing coordinated, rhythmic movements modulated by task and cycle phase as well as a degree of supraspinal influence.[6,37,183] The cervical component of the human networks effecting arm swing is thought to reside at level of the cervical enlargement, with inputs from the lower limb circuits in the lumbar enlargement conducted along long propriospinal pathways and via local segmental propagation of rhythmicity in the thoracic cord.[36,145,146,177,184] It may therefore be hypothesised that an incomplete injury rostral to the cervical circuits will render arm swing less sensitive to changes in supraspinal drive arising from dual-task performance, while a thoracic injury partially disrupting inter-segmental networks would result in heightened sensitivity to cognitive modulation. We employed an established dual-task paradigm based on the Stroop task in patients with incomplete thoracic or cervical SCI and matched controls to assess the changes in arm swing asymmetry brought about by increases in cognitive load while walking.

3.3 Materials and methods

This study, approved by the cantonal ethics committee of Zurich (KEK-2014/0004), was carried out at Balgrist University Hospital in accordance with Good Clinical Practice and the Declaration

of Helsinki. Patients with spinal cord injury able to walk on a horizontal treadmill without hand rail support were consecutively recruited via mailed flyers and during hospital visits. To ensure they could walk at a speed at which stable 1:1 arm swing movements are usually produced,[185] all patients were required to demonstrate a maximal overground walking speed of at least 3.5kmh^{-1} as measured during the 10m walk test (10MWT). Controls were drawn from a pool of healthy subjects who had previously undergone an identical protocol and matched 1:1 with patients based on age, gender, height and weight. All participants gave informed, written consent.

At a first session, subjects were screened for any significant orthopaedic, neurological, cardiac or pulmonary abnormality other than the existing spinal cord injury in patients. Colour-blind participants were also excluded. Patients underwent a full neurological assessment including ASIA impairment scale (AIS) scoring.[186] Patients were grouped as cervical or thoracic based on whether or not the lowest component of their cord lesion on MRI was below the anatomical C8 level. Included subjects then underwent a 40-minute acclimatisation protocol on the treadmill which included four 45-second rehearsals of the different dual-task conditions. Subjects were blinded to the purpose of the study.

Within 7 days, participants returned for full-body gait analysis. The 10MWT[42] and the timed 25-foot (25FWT)[43] were performed. The mean maximal overground speed was calculated from the mean of two 25FWT attempts. Three-dimensional gait analysis was conducted while walking on an instrumented treadmill (120Hz, FDM-T, Zebris Medical GmbH, Germany) in a clinical gait laboratory equipped with ten infrared cameras using Nexus 1.8.5 (Vicon, Oxford, UK) at a sampling rate of 200 Hz. An extended full-body Plug-in-Gait marker set (Vicon, Oxford, UK) was applied to the participants for motion tracking.

Subjects performed all trials barefoot without handrail support on the treadmill at 50% of their mean maximal overground walking speed as assessed in the 25FWT.[187] Participants were asked to fixate on a black cross displayed at eye height in the middle of a monitor positioned in front of the treadmill. Trials were repeated if the subject was observed to touch the hand rails or

make undesired, goal-directed arm movements (e.g. nose scratching, adjusting hair). Stable gait was recorded over a period of 45 seconds.

Cognitive load was added using a modified Stroop paradigm.[57,58] In place of the black cross displayed during the normal walking tasks, text spelling out four colours (red, green, yellow and blue) was presented at pseudorandom intervals using Powerpoint 2010 (Microsoft Corp., Redmond, WA, USA). The duration of presentation of each stimulus was between 600 and 1400ms (mean 1Hz). The task was presented in the participant's self-declared native language and script. In the congruent Stroop condition, the colouring of the text was consistent with that of the colour spelled out in the text. In the incongruent condition, all stimuli consisted of spelled colours presented in one of the four index colours not corresponding to the written stimulus.

Raw data were reconstructed and labelled semi-automatically in Nexus. Lower body gait cycle events were set using data exported from the force-plate under the treadmill. Arm swing cycle was defined by the maximal protraction and retraction of the wrist joint centre. Final data were then screened in ProCalc 1.1 (Vicon, Oxford, UK) for undesired arm movements by identifying cycles in which the wrist centre was raised above the level of the sternum in the vertical axis. Cycles including such movements and the preceding and subsequent three cycles were removed from the analysis. Final data was processed using ProCalc to output spatiotemporal gait parameters for all trials.

The three-dimensional trajectory of a point half way between the two wrist markers was the principal measure of arm swing.[139] The arm swing asymmetry index (ASI) is expressed as follows;[138,151]

$$ASI = \left(\frac{L - R}{max(L, R)}\right) \times 100$$

in which *L* is the wrist trajectory on the left and *R* that on the right, giving an index value between -100 and 100, with 0 representing perfectly symmetrical movements and trials in which the wrist trajectory was longer on the right than the left would yield a negative index, and vice versa.

Differences in demographic data between groups was assessed for statistical significance using Wilcoxon signed rank tests. The ASI values for each group were analysed statistically

using a non-parametric Friedman analysis in which condition was a repeated measure. A Kruskal-Wallis test was used to assess differences across the three groups. When these returned significant results, pairwise post-hoc Wilcoxon signed rank tests were performed with Dunn-Bonferroni correction for multiple comparisons. Relationships between ASI at baseline and ASI change under the different walking conditions with age, sex, time since injury, asymmetry of upper limb impairment (calculated from the left and right upper extremity motor scores [UEMS] in the same manner as the ASI) and step length asymmetry was assessed using Spearman's rho and likewise corrected for multiple comparisons. Statistical significance was set at $p \leq 0.05$ for all tests.

3.4 Results

Six patients with a cervical SCI (one female), six with a thoracic SCI (two female) and 12 matched control participants were recruited. Patient and control subject characteristics are summarised in Table 1. Although mean UEMS was lower in the cSCI group (48.5 vs 50), this difference did not reach significance ($p = 0.059$). Likewise, there were no significant differences between the groups in terms of LEMS, UEMS & LEMS laterality, other clinical scores or time since injury; all patients were classified as AIS D. The patient groups walked on the treadmill at similar median speeds (set as 50% of their maximal overground speed: cervical patients; 3.1 kmh^{-1}, IQR 1.22, thoracic patients; 2.95 kmh^{-1}, IQR 1.05), which was significantly slower than the controls (4.0 kmh^{-1}, IQR 1.22; $p \leq 0.000$).

All patients and control subjects exhibited one arm swing cycle per lower limb gait cycle during normal treadmill walking. During normal walking, the length of the mean wrist trajectories on the left and the right during normal walking were not significantly different between the control and either of the patient groups (Figure 1). In all three walking conditions, left arm wrist trajectory was consistently larger than that on the right and this discrepancy became significant in the tSCI group under the incongruent Stroop task ($p = 0.014$).

Accordingly, mean(±SEM) ASI during normal walking was 13.7±6.3, 14.2±10.7 and 15.8±6.0 in the controls, cervical and thoracic patients respectively, indicating arm swing movements that were proportionally smaller on the right. These values increased to 16.6±6.4 and 23.4±3.8 in the controls and thoracic patients during the congruent Stroop task. In both these groups, the performance of the incongruent Stroop task was associated with a further increase, to 19.6±7.8 in the controls and 30.7±4.4 in the thoracic patients. In contrast, mean ASI in the cervical patients decreased to 9.3±13.5 and 6.0±12.9 in the congruent and incongruent Stroop tasks, respectively (Figure 2).

The relative effect of the concurrent Stroop tasks on the ASI during gait was evaluated. Control subjects showed a modest increase (i.e. towards further left-sided dominance of arm swing movements) from the baseline normal walking task of 2.4±3.5 in the congruent Stroop task and subsequently to 6.5±3.8 during the incongruent task (Figure 3). Equivalent values in the cervical group were -4.8±3.9 and -8.2±6.0, while the decrease in right arm swing in the thoracic group resulted in ASI changes of 8.4±4.2 and 12.5±6.3 in this group. The changes in ASI brought about by the incongruent Stroop task in the cervical and thoracic groups were significantly different ($p=0.011$).

Patient	Age (y)	Gender	Handedness (before injury)	Height (cm)	Weight (kg)	Classification		Radiological extent of lesion	ISNCSCI LEMS		ISNC SCI UEMS		UEMS laterality index	ISNCSCI light touch		ISNCSCI pin prick		Modified Ashworth scale		Time since injury	Aetiology	T25FW (s)	10MWT (s)	6MWT (m)	Walking speed (km h^{-1})
						Level	AIS		Right	Left	Right	Left		Right	Left	Right	Left	Right	Left						
1	45	F	R	174	92.0	T10	D	T5 – T7	25	25	25	25	0	43	43	55	49	0	0	12 months	Ischaemic	4.19	6.57	582	3.1
2	29	M	R	174	78.3	T11	D	T11 – L2	24	20	25	25	0	56	56	47	49	0	0	3 months	Traumatic	6.06	7.74	402	2.5
3	40	F	R	165	58.0	T10	D	T7 – 8	25	24	25	25	0	45	56	49	56	0	0	6 years	Traumatic	4.70	6.20	500	2.8
4	43	M	R	172	76.2	C4	D	C3 – 4	20	20	24	24	0	11	8	9	8	5	6	13 years	Traumatic	5.35	6.99	435	2.8
5	41	M	R	169	67.1	C6	D	C6	25	25	25	25	0	55	56	56	56	0	0	12 years	Traumatic	4.24	5.64	683	3.4
6	41	M	R	176	81.2	C5	D	C5-6	20	24	22	23	4.35	40	50	50	34	3	6.5	4 years	Traumatic	8.57	11.46	295	1.9
7	56	M	R	178	78.2	T12	D	L2	25	25	25	25	0	47	47	56	47	0	0	4 years	Traumatic	3.49	4.64	652	3.7
8	39	M	R	183	85.0	T1	D	T1-3	25	25	25	25	0	56	46	35	50	0	3	3 years	Traumatic	4.71	6.14	520	3.1
9	48	M	R	176	77.3	C3	D	C2-4	24	24	25	25	0	56	56	53	56	0	4.5	8 years	Traumatic	4.13	5.52	620	3.4
10	50	F	R	160	57.4	C6	D	C5-6	25	25	25	25	0	56	56	56	33	0	0	15 months	Traumatic	5.07	6.69	494	3.1
11	35	M	R	171	78.0	C4	D	C3-6	22	25	18	21	14.3	56	33	56	35	5	0	7 years	Traumatic	5.52	7.44	461	2.5
12	65	M	R	167	66.0	T11	D	T4-6	25	25	25	25	0	56	46	52	52	2	0	9 years	Tumour	8.15	6.20	441	2.2

Table 3.1. **Patient characteristics.** AIS; American Spinal Injuries Association Injury Score, ISNCSCI; International Standards for Neurological Classification of Spinal Cord Injury, LEMS; Lower Extremity Motor Score, UEMS; Upper Extremity Motor Score, T25FW; timed 25-foot walk, 10MWT; 10 metre walk test, 6MWT; 6-minute walk test.

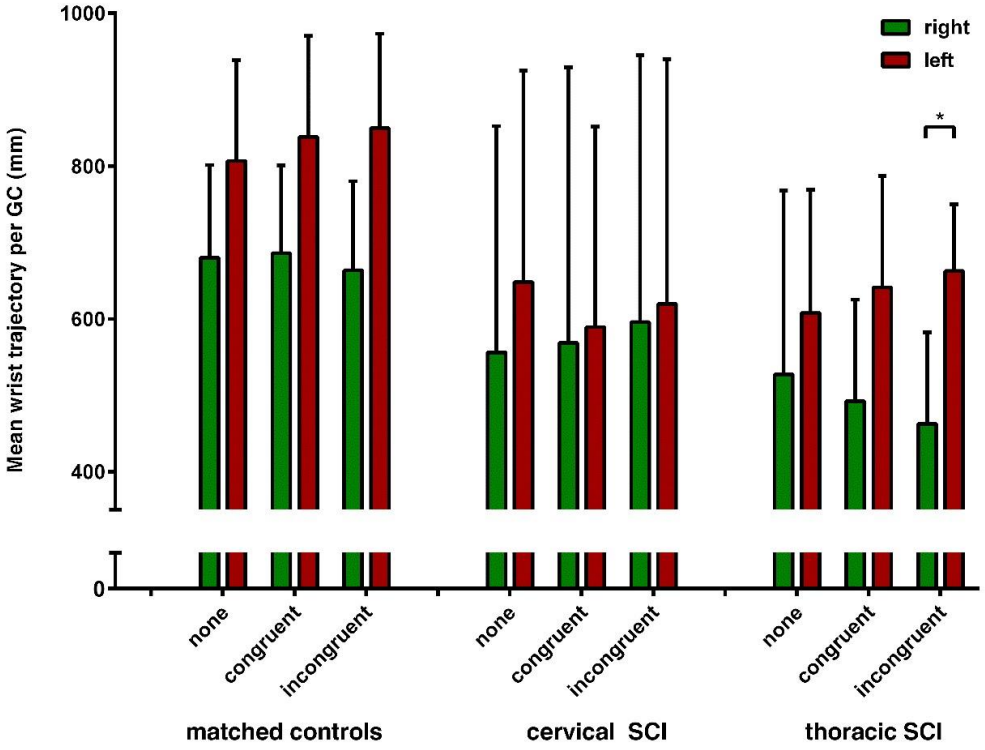

Figure 3.1. Absolute wrist trajectory length. Mean, three-dimensional wrist centre trajectories for six patients with cervical SCI, 6 with thoracic SCI and 12 matched controls under increasing levels of cognitive load in a treadmill dual task. GC; gait cycle. Error bars indicate standard deviation. Statistical significance was determined using a repeated measures Friedman analysis with post-hoc Wilcoxon rank sum tests. P values were corrected for multiple comparisons within each group using the Dunn-Bonferroni method.

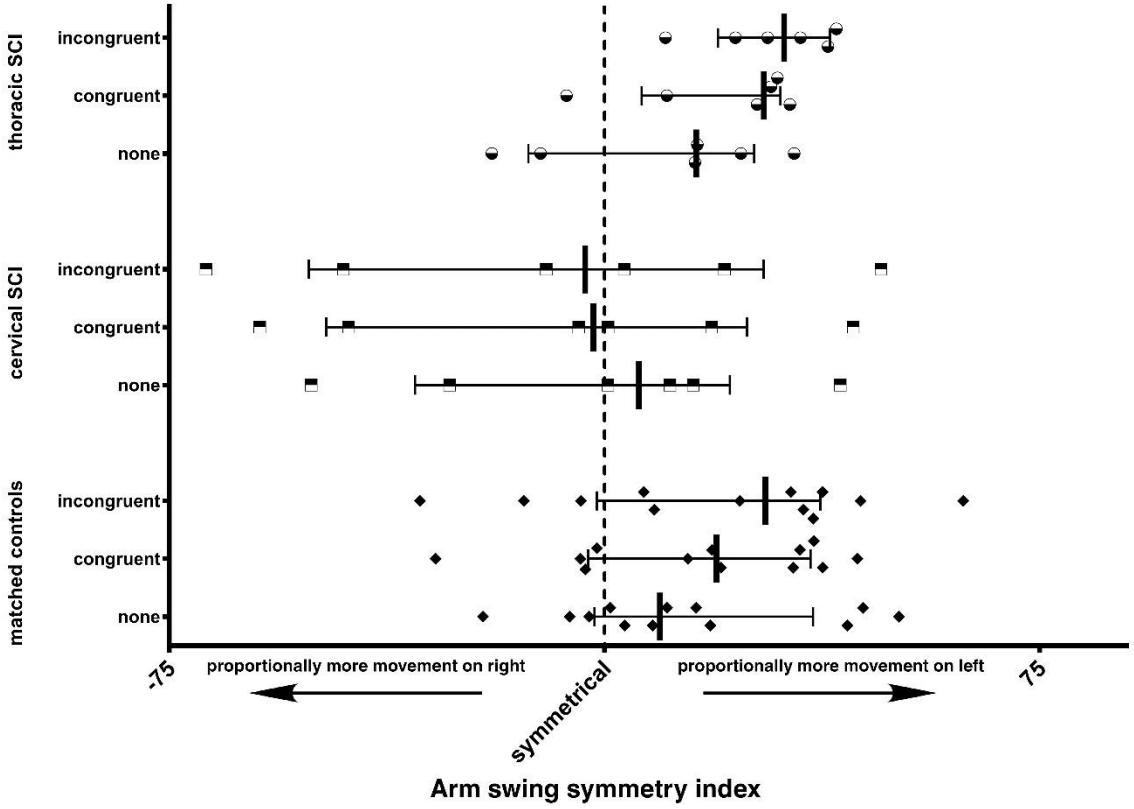

Figure 3.2. Arm swing asymmetry index (ASI) under increasing cognitive load. Wrist trajectory asymmetry index is calculated using the left and right 3D wrist centre trajectories, with left dominance resulting in a positive value and vice versa. ASI is given as the mean value per gait cycle over a trial of 45 seconds (approximately 34 gait cycles at 3.1kmh-1). In the trial with no additional task, participants looked directly ahead at a black cross in the centre of a screen placed at eye height. Median ASI with 95% confidence intervals is shown, with individual ASI results indicated for each condition and subject group.

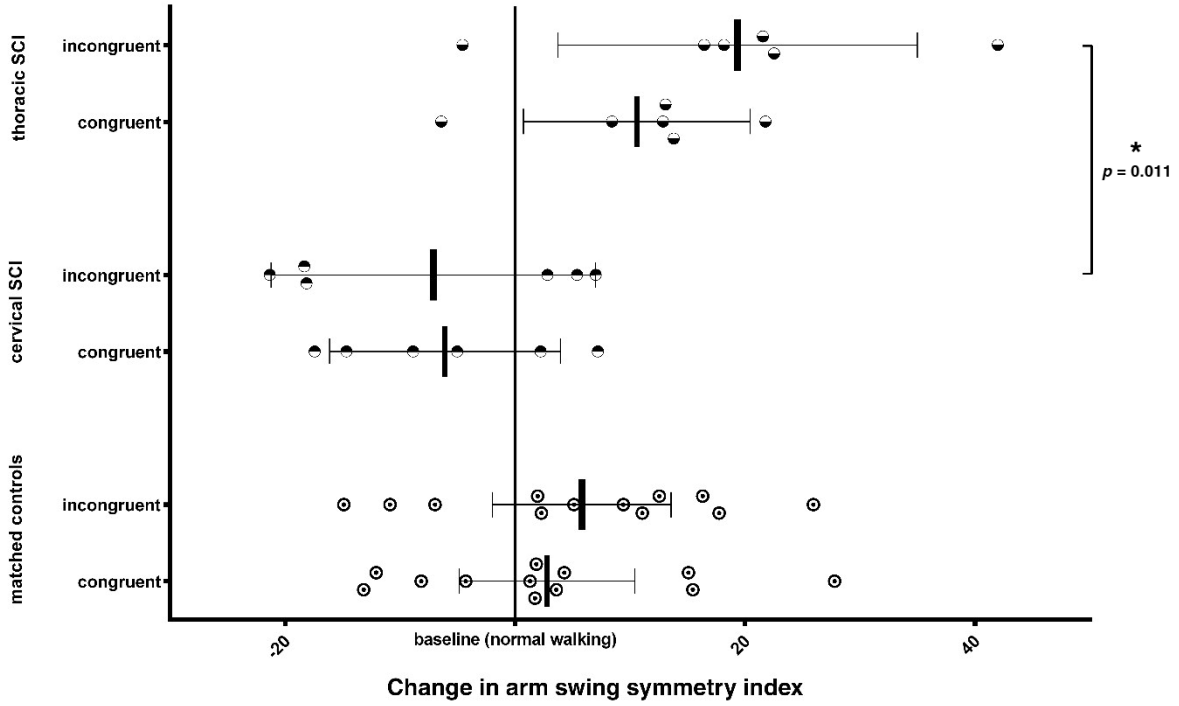

Figure 3.3. Change in ASI under congruent and incongruent Stroop tasks. Median ASI change with 95% confidence intervals show deviation from baseline ASI recorded during normal walking. Statistical significance was determined using a Kruskal-Wallis analysis with post-hoc Wilcoxon rank sum tests. P values were corrected for multiple comparisons within each group using the Dunn-Bonferroni method.

3.5 Discussion

Recently, it has been shown that the symmetry of arm movements during gait can be modulated during cognitive dual tasks,[137] particularly the Stoop task.[138] A paucity of arm swing on the right may be accounted for by reallocation of supraspinal resources during dual-tasking away from the maintenance of arm swing; it is pronounced in older adults, in whom cognitive resources are degraded.[137,138] Precisely why the right side is more sensitive to this effect is unclear, but is likely due a reduction in corticospinal drive resulting either from interference stemming predominantly from left hemisphere language processing, differential degrees of connectivity to the dominant and non-dominant arms, heightened sensitivity to interference within the dominant hemisphere, or a combination of these factors. All our patients and controls were right-handed, precluding testing of hypotheses related to language hemisphere dominance. A previous report examined the effect of handedness on ASI in a small cohort and under varying locomotor (but not dual-task) conditions and concluded that ASI was not related to handedness,[151] although as the majority of left-handers and virtually all right-handers have language centres in the left hemisphere, further study in truly right-lateralised individuals or larger samples may be more revealing.

Arm swing has been relatively neglected as a feature of ambulatory behaviour in patients with incomplete SCI (iSCI). The most thorough studies of upper limb kinematics in iSCI aimed to establish the presence or absence of arm swing in iSCI. These rather heterogeneous samples included relatively poor walkers in whom arm swing deficits may have been significantly affected by lateralised pathology, spasticity or habituated use of walking aids.[188,189] In order to investigate the modulation of arm swing asymmetry in the context of spinal lesions, we attempted to recruit a more homogenous group of patients who, despite their iSCI, were able to produce near-normal walking patterns including bilateral arm swinging on the treadmill at a comfortable walking speed. The patient groups were closely matched, with median speed and wrist trajectory and clinical and demographic parameters similar in cervical and thoracic patients (Table 3.1).

Control participants exhibited a trend towards more left-dominant arm swing under increasing cognitive load against a background of significant variability, in keeping with previous studies in healthy subjects.[137,138,151] Cervical patients showed no such leftward tendency, and wrist trajectories remained essentially the same on the left and the right under all three conditions. Patients with thoracic lesions, however, showed a considerably more homogenous response to the Stroop tasks than the other groups, driven by the significant reductions in arm swing on the right side.

These findings fit well with the current understanding of interlimb coordination in humans, in which locomotor patterns emanating from the lumbar enlargement are coupled via long propriospinal and short intersegmental pathways with their cervical counterpart circuits, with the latter functionally subservient to the former.[145] Disruption of these thoracic pathways in patients with lesions below T1 may result in an adaptive, greater supraspinal role in the maintenance of arm swing, with right arm swing thus significantly more sensitive to cognitive interference from a left hemisphere dual task. Interpretation is more complicated in our cohort of cervical patients in whom four had lesions which extended below C4, which may have directly disrupted the motor pools projecting to the arm muscles. It is therefore not possible to conclude with certainty what underlies the lack of a coherent response to cognitive modulation seen in the cervical patients, although they certainly do not exhibit the homogenous behaviour of those with thoracic injuries.

This study is limited by its small sample size and preliminary nature. Future studies should include the use of upper limb EMG to better characterise what drives the reduction in right arm swing seen in thoracic patients. Specific methodological issues include the use of relative speed matching between the control and patient groups. Walking speed on the treadmill was based on each individual's maximal overground walking speed, used as an outcome measure to quantify overall walking function in the clinical setting[187] and at which the automaticity of arm swing is likely to be strongest. Thus, healthy subjects, as well as patients with different degrees of walking dysfunctions, walked at a speed that was proportional to their walking ability and which was perceived as comfortable by all participants. While this objective method of speed definition is advantageous in challenging participants with dissimilar walking dysfunction to a

proportional degree, different absolute walking speeds may affect cognitive load on arm swing symmetry. This aspect has not been fully addressed, but Plate et al observed that, although absolute arm swing amplitude increases with speed, ASI is preserved across a range of walking speeds.[138]

We allowed all participants to gain a degree of familiarity with the task during acclimatization. This familiarization was the same for each participant

Both the patient and control groups exhibited a degree of arm swing asymmetry during normal walking. While such spontaneous asymmetry may be explained in certain cervical patients as a consequence of an asymmetrical injury, its marked presence in healthy controls and thoracic patients is more difficult to account for. Moreover, the degree and direction of baseline asymmetry in the patients with relatively mild cervical injuries here was not correlated with lateralised UEMS. This inherent variability in ASI has implications for the usefulness of arm swing asymmetry as a diagnostic parameter or clinical trials outcome measure, although within subjects, the use of cognitive load modulation during walking appears to be a potential method for estimating the degree of supraspinal contribution to arm swing. Further refinement of both the dual-task methodology employed and perhaps the gait parameters used to define arm swing and ASI may lead to a clinical or research application of this interesting phenomenon.

Chapter 4: Spontaneous resolution of an extensive post-traumatic syrinx

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Author contributions

TK: acquisition of data, literature review, drafting and critical review of manuscript

JR: acquisition of data, literature review, drafting and critical review of manuscript

4.1 Introduction

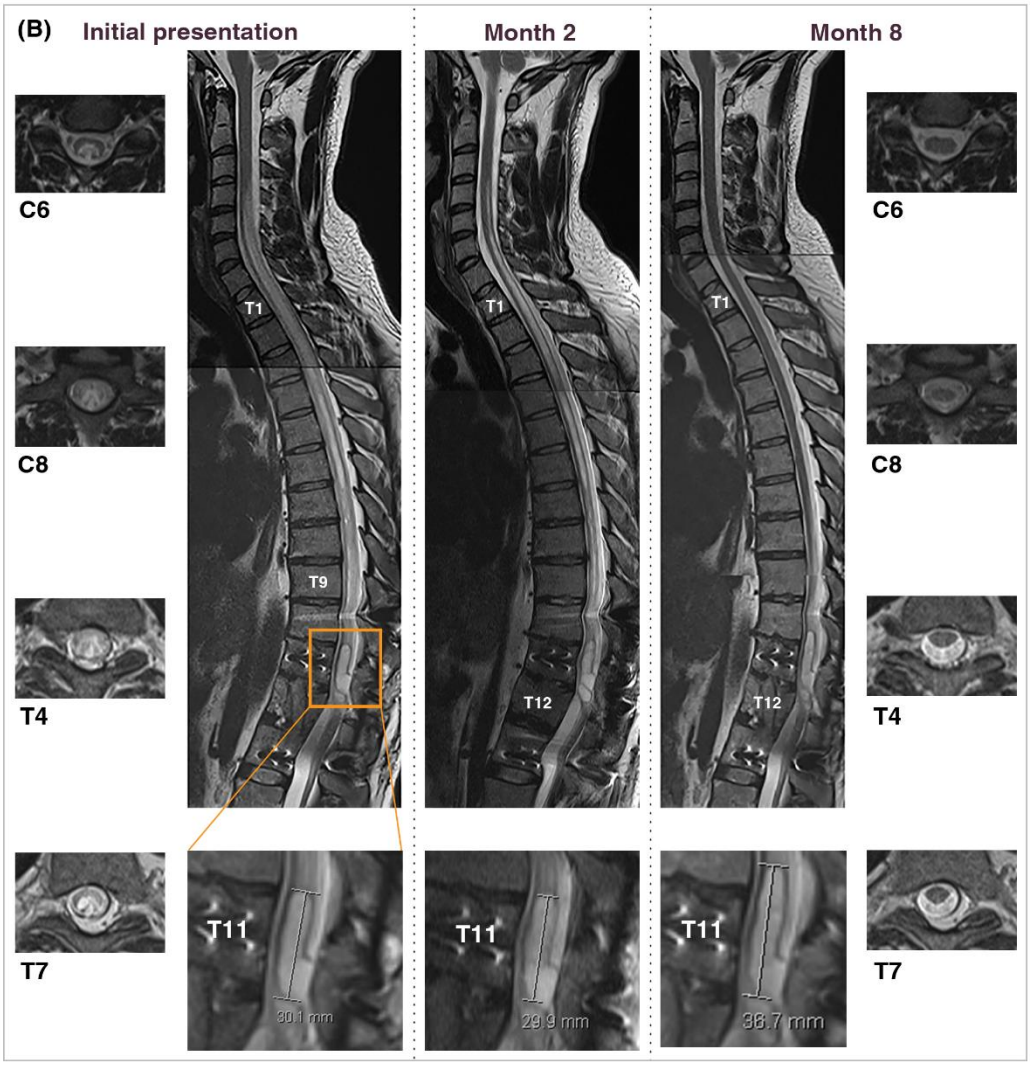
The prevalence of symptomatic syringomyelia in patients with chronic spinal cord injury (SCI) is around 4.5%.[190] It is an important cause of treatable neurological deterioration, although surgical shunting of the syrinx or arachnoid adhesiolysis of tethered elements have unpredictable results.[191] Classically, syrinx extension causes progressive neuropathic pain, often with dissociated sensory loss due to compression of the more central, spinothalamic projection neurons with relative preservation of dorsal column function. We report an unusual case of the total, spontaneous resolution of an extensive cervicothoracic syrinx cavity in a patient with symptomatic, post-traumatic syringomyelia (PTS) and describe the changes in contact heat evoked potentials (CHEPs) associated with its development and disappearance.

4.2 Case Report

A 32-year-old male with a chronic incomplete SCI (AIS C, sub T9) resulting from a motorcycle accident presented 9 years after the initial trauma with acute-onset, neuropathic pain in the right shoulder blade and upper limb following an episode of heavy coughing. Cardiovascularly fit, he was a keen wheelchair sportsman. Extensive dissociated sensory loss was documented in dermatomes C6 to T10 on the right with impaired pin prick sensation but preserved light touch (Fig. 4.1A). Whole-spine magnetic resonance images (MRI) were in keeping with a mature thoracic syrinx cavity, with less well-delineated cord signal change extending cranially to segments C3/4 and a pre-existing, post-traumatic cyst at T11 (Fig. 4.1B). Neurophysiological assessment demonstrated impaired CHEPs at C6 and C8 bilaterally (Fig. 4.1C) with preserved dermatomal somatosensory evoked potentials. Inflammatory and ischemic aetiologies were

(A)

AIS	Baseline (L/R)	Initial Presentation	Month 2	Month 8
Motor (max. 50 / 50)	37 / 39	37 / 39	37 / 39	37 / 39
Light touch (56 / 56)	48 / 48	48 / 46	48 / 48	48 / 48
Pin-prick (56 / 56)	50 / 42	50 / 31	50 / 27	50 / 40
Motor level	L2	L2	L2	L2
Sensory level	L1	C6	C6	T12



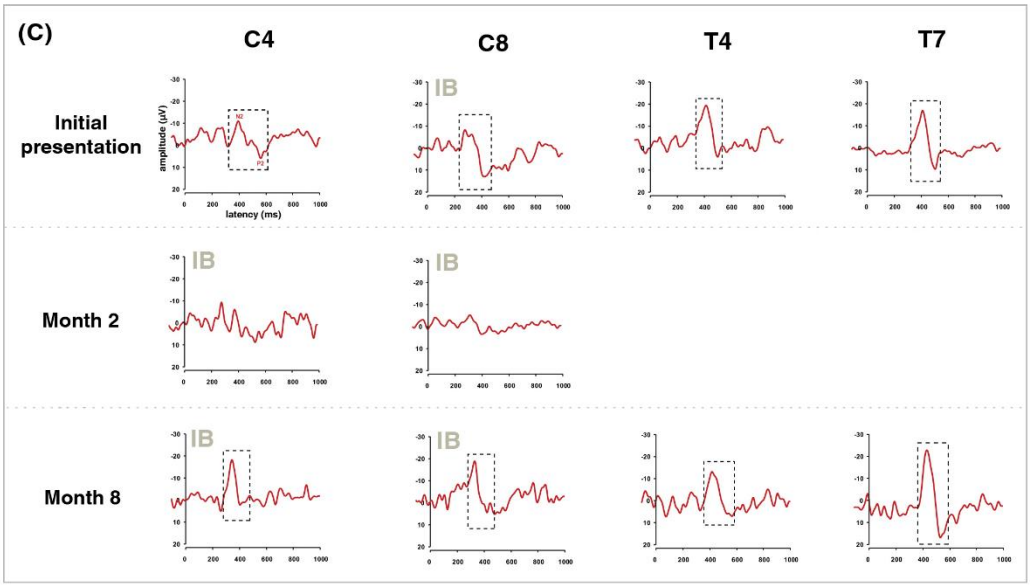


Figure 4.1 Clinical, neuroimaging and electrophysiological findings in a spontaneously resolving, post-traumatic syrinx. (A) American Spinal Injury Association (ASIA) impairment scale (AIS) at four time points (clinical baseline 2 years post-injury, at index presentation and 2 and 8 months later) in a 32-year-old patient with a chronic, incomplete (AIS C, neurological level sub T9) spinal cord injury who presented with a symptomatic post-traumatic syrinx. (B) T2 MRI images of the same patient are presented from left to right from index presentation and 2 and 8 months later. No previous MRI was available. Between presentation and 2 months, sagittal cervicothoracic spine studies show the development of the syrinx which extended from segments C3/4 to an interface with an existing posttraumatic cyst at the T11 vertebral level. Axial insets show the full extent of the syrinx cavity. Zoomed sagittal images at the T11 level at the bottom of the figure document a 5mm rostral expansion of the pre-existing posttraumatic cyst associated with the spontaneous disappearance of the syrinx. (C) Contact heat evoked potentials (CHEPs) at the same time points as the imaging above on the more symptomatic, right side. Presented potentials are means of 15 trials at a given dermatome. If a trial resulted in an impaired or abolished response at a baseline temperature of 35oC, this was increased to 42oC.7 The responses at the highest baseline temperature used are presented. Dermatomal somatosensory evoked potentials were consistently normal at all time points (not shown).

considered but deemed highly unlikely due to the relatively mild symptoms in the context of such extensive cord involvement. After 2 months of watchful waiting and with no improvement in symptoms, whole spine MRI was repeated. The syrinx cavity had consolidated in the cervical cord and CHEPs were abolished at C6 and C8 bilaterally. Six months later, while awaiting surgical adhesiolysis, the patient again underwent MRI and electrophysiology after reporting sudden symptomatic improvement over the course of a few days. The cervicothoracic syrinx had completely resolved and CHEPs improved, while the rostrocaudal dimension of the post-traumatic cyst had increased from 30mm to 37mm. The neuropathic pain was significantly improved and only subtle abnormalities of protopathic sensation remained in the right arm. Findings remained stable at 9 months (Supp. Fig. 4.1).

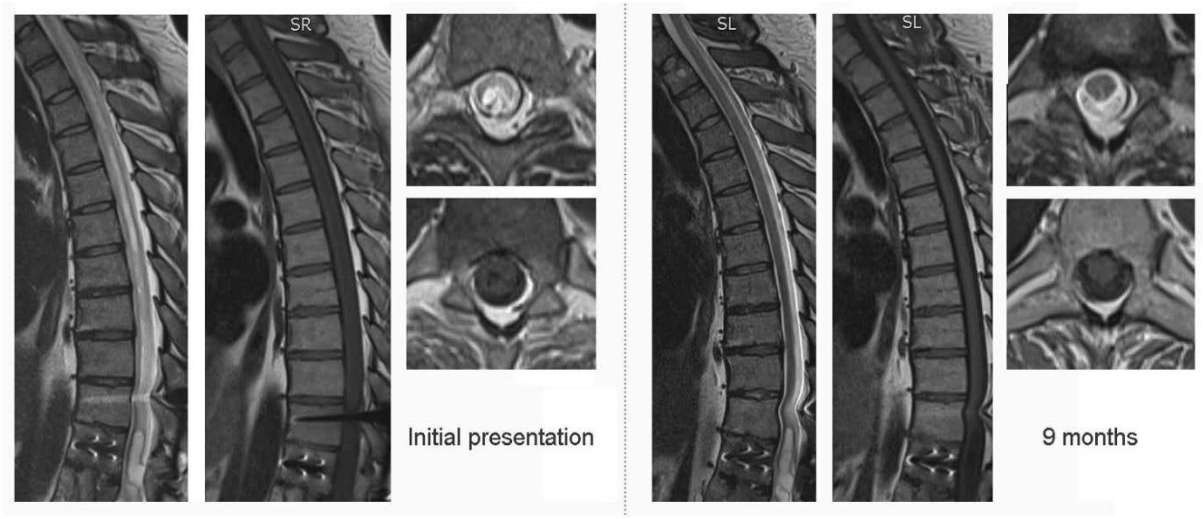
4.3 Discussion

In the most widely-accepted theory of PTS, the antecedent cause of syrinx formation is subarachnoid block due to arachnoid adhesions at or near the level of prior injury.[191–193] Patients

with PTS have reduced thecal compliance and higher pressures in the subarachnoid CSF at cardiac systole drives CSF into the cord through perivascular spaces.[192] *In vitro* simulations of subarachnoid stenosis in PTS suggest that caudocranial syrinx extension results from ballooning of the rostral cavity during episodes of increased intracompartmental pressure, as occur on coughing.[193] Such expansion likely proceeds relatively atraumatically along tissue planes and may account for the often subtle symptomology encountered, even in anatomically extensive PTS.[194] The sudden and complete radiological resolution of a syrinx, accompanied by subtotal clinical recovery, is almost without precedent. Interestingly, the only similar report also featured a post-traumatic cyst and the authors suggested that resolution resulted from a rupture of the syrinx cavity into the subarachnoid space.[195] A similar rupture into the cyst may account for the observed increase in its size in this case. Our patient was involved in regular, strenuous sports which he had to curtail as a result of syrinx-related pain. Perhaps a degree of subarachnoid block not quite sufficient for syrinx formation in a sedentary individual may result in PTS in the context of heavy exercise. As such, it may be reversible when exercise is reduced, although with a high risk of recurrence.

CHEPs are performed using a contact-thermode stimulator on a dermatome to elicit EEG responses.[196] The thermal stimulus specifically activates Aδ nociceptors in the periphery and is propagated through the spinothalamic tract, which is specifically vulnerable in the case of an axially expanding, central syrinx, where horizontally crossing commissural fibres are more susceptible to damage than the longitudinal tracts of the dorsal columns.[194,196] As PTS is invariably non-communicating with respect to the central canal, the path of expansion may meander somewhat eccentrically within the cord and this likely accounts for the sparing of spinothalamic function at T4 and T7 seen in this case, where axial images reveal the body of the syrinx to be more dorsally located (insets, Fig. 4.1B).

In conclusion, spontaneous resolution in PTS is rare but possible and seems to be associated with sizeable post-traumatic cystic lesions, which may represent a therapeutic target in selected cases. CHEPS are ideally suited to the assessment of syringomyelia, in which a central syrinx tends to preferentially affect the small crossing fibres in the anterior commissure and may serve as an early marker of disease progression.



Supplementary Figure 4.1. T1 and T2-weighed images at index presentation and 9 months later. The left panels show sagittal thoracic MRI findings at index presentation with an extensive central area of increased T2 (left) and decreased T1 (centre) signal change within an expanded cord. Axial images at the T7 vertebral level (T2; above right, T1; below right) show a loculated, fluid-filled lesion within the cord consistent with a mature, complex syrinx. The right panels show the same patient 9 months later, revealing full, spontaneous regression of the syrinx.

Task-specific responses in locomotor readouts

Technological developments in diverse biomedical fields are permitting the investigation of the human central nervous system at higher spatial and functional resolutions than ever before. Contact heat evoked potentials (CHEPs) reveal highly specific deficits in the spinothalamic tracts[196–198] (**Chapter 4**), while structural magnetic resonance imaging demonstrates modality-specific atrophy in the brain and spinal cord after spinal cord injury.[199–201] Novel biomarkers obtained in this way may help to accurately diagnose neuropathology, monitor rehabilitation or select patients for clinical trials of treatments aimed at promoting neural regeneration and repair.[202,203]

Such investigational specificity for the neuroanatomical systems that contribute to locomotor behaviour and lesions within them is a considerably more challenging proposition. Although the technical capability for measuring human movement in precise detail at high sampling rates is now well-developed,[45] walking is a highly dynamic process with multiple degrees of freedom available to each body segment and gait patterns and parameters may vary greatly between individuals and within individuals walking at different speeds.

Zörner *et al.* addressed this sensitivity problem in rodents by comprehensively profiling animals as they undertook four different locomotor tasks and demonstrated that particular tasks and outcome measures were more sensitive to the presence of a lesion in a given part of the CNS.[49] In the present thesis, we applied a similar approach, adapted to humans, using 3D kinematic gait analysis to measure the response in certain gait parameters in an individual as walking conditions are imposed which selectively challenge a system of interest at a fixed, comfortable speed. In doing so, we minimise the problem of inter-individual differences in gait parameters and focus instead on the effect that a locomotor condition, for instance cognitive loading, exerts on a particular group of individuals compared to normal walking, such as older adults or patients with incomplete SCI.

We were able to show that even crucially important aspects of foot end-point control are degraded by additional cognitive demands and removal of visual cues (**Chapter 1**) and observed novel, task-specific responses to cognitive load in arm swing asymmetry in healthy control participants (**Chapter 2**). An initial application of our cognitive load paradigm to patients with incomplete SCI (**Chapter 3**) revealed that these task responses are altered by the level of the spinal lesion relative to the cervical CPG components.

Minimum toe clearance frequency distributions

Our analysis of the frequency distributions of minimum toe clearance under several walking conditions (**Chapter 1**) revealed that this important gait parameter is sensitive to an apparent decline in endpoint control associated with ageing, but only revealed under heavy cognitive loading and, to a lesser extent, visual restriction. This is a clear example of the advantages of condition-based gait analysis. Mean minimum toe clearance is relatively insensitive to ageing or disease status but its response to visual restriction and cognitive loading in ageing renders it a useful clinical diagnostic marker. Analysis of frequency distributions unveils intermittent, impaired control of the toe trajectory which significantly increases modelled tripping risk. Both of these approaches will now be implemented in SCI and multiple sclerosis cohorts and evaluated as readouts for gait deterioration and recovery as well as indicators of an increased risk of falling.

Cortical control of arm swing behaviours

Arm swing feels like a highly automatic component of human walking behaviour and it is tightly coordinated with the lower limb gait cycle, suggesting a predominantly spinal control mechanism mediated by rhythmic CPG networks.[36,156,204,205] Our results (**Chapter 2**) suggest that the reality is more nuanced, providing evidence that a supraspinal influence to the maintenance of right arm swing[37] is subject to unilateral interference through the left-lateralised Stroop task.

Our findings revealed the predicted increase in susceptibility to arm swing modulation through the Stroop task as participants aged. Surprisingly, a strong gender difference was discovered, with healthy young women resistant to the cognitive-motor interference brought about by the Stroop task. While these findings may be the result of superior cognitive control in young women, our data and those of previous studies suggest no marked gender difference in Stroop task performance.[57,206,207] Thus, it appears that gait control may be subject to hormonal influences that change throughout life and perhaps throughout the menstrual cycle. Adding salivary assessment of oestrogen levels while assessing the Stroop arm swing response in a similar protocol may provide clarity on this controversial finding. Potentially, oestrogen administration may mediate improved gait control in patients with cognitive impairment via promotion of plasticity and redundancy in the prefrontal cortex.[168,170,171,208]

If confirmed and reliable, this phenomenon may allow the study of elements of human locomotor control *in vivo*, for instance, by performing bilateral electromyography in the upper arm muscles with and without an additional Stroop task while walking to determine whether the cortical control of arm swing is limited to one phase of arm swing. Cortical distraction may even allow the unmasking of attributes of the human cervical CPG and task-dependent neuronal coupling[156] between the arms and legs through the comparison of EMG responses to tibial nerve stimulation in the two swinging arms.

Arm swing asymmetry is increasingly being recognised as a useful marker in Parkinson disease.[139,148,156,209,210] We provide initial evidence (**Chapter 3**) that modulating arm swing asymmetry with cognitive loading during the Stroop task may be an indicator of thoracic spinal cord integrity.[108] We were able to show that patients with thoracic SCI were significantly more sensitive to the Stroop dual-task than those with cervical injuries. If further research shows ASI to be reliably reproducible over time, it may have a role as a marker of disease progression or treatment response in patients with thoracic spinal lesions.

Completing the gait profile: body weight support and skilled walking

In terms of outlook, two further tasks will be added to our gait profiling paradigm. The first is body-weight support using a transparent robotic system (the FLOAT, Lutz Medical Engineering, Zurich, Switzerland) to unload the patient to a specific percentage (10-50%) of their unloaded body weight while walking on the treadmill.[211] This is analogous to the support given by buoyancy during wading in previous animal studies, [49] and has been shown to facilitate CPG-driven stepping in rodents.[13,212] An optimal balance between support for paretic muscles and proprioceptive loading for spinal locomotor drive may allow patients with SCI to improve their stepping capacity[213] and provide a more sensitive means of measuring changes in locomotor performance over time.

Finally, we have developed a skilled walking task (z-Beam, University Hospital Balgrist, Zurich) in which patients attempt to step on targets projected onto the surface of a moving treadmill (FDM-T, Zebris, Germany) while walking at a comfortable speed. Targets are presented in a pseudorandomised sequence and stepping accuracy is measured by automatically comparing the position of each projected target with the patient's foot position recorded on a force-plate underlying the treadmill belt. Mean accuracy and step-to-step variability provide a direct measure of the effectiveness of targeted stepping.

Skilled walking is a sensitive measure of overall spinal cord integrity[49,214] as it relies on unimpaired function of most key pathways, particularly the corticospinal tract and dorsal columns. It is therefore reasonable to expect it to be a sensitive indicator of locomotor function and to scale with disease severity.

These tasks complete the comprehensive battery of treadmill gait analysis tests that we have been developing and are currently employed in clinical and research applications at University Hospital Balgrist and University Hospital Zurich.

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Curriculum vitæ

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Education and work experience

01.11.2016 – present	**Resident in Neurosurgery**
	Department of Neurosurgery
	Cantonal Hospital St. Gallen
	(Director: PD. Dr. med. Astrid Weyerbrock)
01.07.2013 – 31.10.2016	**MD-PhD Student**
	Spinal Cord Injury Center
	University Hospital Balgrist
	(Director: Prof. Dr. med. Armin Curt, FRCPC)

01.12.2012 – 31.10.2016	**Resident in Neurosurgery (50%)** Hirslanden Clinic Zurich (Supervisor: Prof. h.c. Dr. med. Evaldas Cesnulis)
11.04.2013	**Membership of the Royal College of Surgeons of England (MRCS)**
12.11.2012 – 05.11.2013	**Anatomy Demonstrator (30%)** Anatomy Institute University of Zurich (Director: Prof. Dr. med. Dr. sc. nat. Oliver Ullrich)
31.01.2011 – 13.12.2011	**Honorary Clinical Senior Lecturer** School of Medicine, University of Otago Wellington, New Zealand
13.12.2010 – 13.12.2011	**Neurosurgical Registrar** Wellington Regional Hospital Wellington, New Zealand (Supervisor: Mr. Agadha Wickremesekera, MD, FRACS)
05.08.2009 – 03.08.2010	**Foundation Year 2 Doctor (Academic Programme)** Royal Free Hospital London, England (Supervisor: Mr. Adrian Fogarty, FRCS, FRCEM)
05.08.2009	**Full licence to practice medicine in the United Kingdom**
06.08.2008 – 04.08.2009	**Foundation Year 1 Doctor** Barnet & Chase Farm Hospitals NHS Trust Enfield, Middlesex, England (Supervisor: Mr Steve Warren, MS, FRCS)

26.06.2008	**Bachelor of Medicine and Bachelor of Surgery (MBChB)** University of Leeds, West Yorkshire, England
01.10.2007 – 01.06.2008	**Student Advisor to the UK Foundation Programme Office** Cardiff, Wales
09.2006 – 06.2007	**Intercalated Bachelor of Science (BSc)** University College, London, England Thesis: Degeneracy and dynamic diaschisis: a case study using fMRI (Supervisor: Prof. Cathy Price, PhD)
06.2004 – 09.2005	**Erasmus Exchange Student** Faculty of Medicine Eberhard-Karls University Tübingen, Germany
09.2001 – 06.2008	**Medical School** Leeds University School of Medicine Leeds, West Yorkshire, England
01.06.2007	**Bachelor of Science (BSc) in Speech Science and Communication** University College, London, England
06.2001	**General Certificate of Education (Psychology, Chemistry, Biology)** Burton College Burton-on-Trent, Staffordshire, England
06.2000	**General Certificate of Education (General Studies)** Rawlett High School Tamworth, Staffordshire, England
09.1999 – 06.2001	**Further education** Burton College Burton-on-Trent, Staffordshire, England

06.1998	**General Certificate of Secondary Education**
09.1992 – 06.1999	**Secondary education** Rawlett High School Tamworth, Staffordshire, England
06.1989 – 06.1992	**Primary education** Flax Hill Primary School Tamworth, Staffordshire, England

Courses and further training

Academic

Molecular Biology Block Course	*Autumn Term 2013*	*University of Zurich*
Medical Immunology Block Course	*Autumn Term 2013*	*University of Zurich*
Development of the Nervous System	*Autumn Term 2013*	*University of Zurich*
Structure, Plasticity and Repair of the Nervous System	*Autumn Term 2013*	*University of Zurich,*
Introductory Course in Neuroscience I	*Autumn Term 2013*	*Centre for Neurosciences, Zurich*
Neuroscience Block Course	*Spring Term 2014*	*University of Zurich*
Introductory Course in Neuroscience II	*Spring Term 2014*	*Centre for Neurosciences, Zurich*
Diseases of the Nervous System Block Course	*Spring Term 2014*	*University of Zurich*
System Identification and Kalman Filtering	*Spring Term 2014*	*ETH Zurich*
Modern Approaches to Neurorehabilitation	*Spring Term 2014*	*University of Zurich*
Statistics for Neuroscientists	*Spring Term 2014*	*University of Zurich*
EXCITE Multimodal Imaging Summer School	*Autumn Term 2014*	*ETH Zurich*
Aspects of Sensory Motor Transformations	*Spring Term 2016*	*University of Zurich*
Research Ethics for Life Scientists	*Spring Term 2016*	*University of Zurich*
Translational Robotics for Clinical Rehabilitation	*Summer 2016*	*ETH Zurich*

Clinical & Others

Media Training Course	*23rd February 2007*	*British Medical Association, London, England*
Advanced Life Support (ALS)	*17th – 18th February 2009*	*Queen's Hospital, Burton-on-Trent, England*
Advanced Trauma Life Support (ATLS)	*1st – 3rd July 2009*	*Surrey County Hospital, Guildford, England*
Introduction to Health Service Management	*August 2009 – July 2010*	*Royal Free Hospital, London, England*
Advanced Paediatric Life Support (APLS)	*22nd – 23rd October 2009*	*Calderdale Royal Hospital, Halifax, England*
Intercollegiate MRCS Part A	*12th January 2010*	*Royal College of Surgeons, London, England*
Midas Rex Drill Workshop	*26th March 2011*	*Medtronic, Inc., Sydney, Australia*
Transcranial Doppler Ultrasound Course	*19 – 20th October 2011*	*Royal Brisbane Hospital, Brisbane, Australia*
Safeguarding Children Level 3	*10th October 2012*	*ACI Training, Chepstow, Wales*
Intercollegiate MRCS Part B (OSCE)	*26th February 2013*	*Royal College of Surgeons, London, England*
Imperial Spine Course	*6th – 8th March 2013*	*Royal College of Surgeons, London, England*
MRI Safety Course	*16th April 2014*	*University Hospital Zurich*
AOSpine Principles Specimen Course (AMTS)	*16th – 17th October 2014*	*Muttenz*
Good Clinical Practice (GCP)	*21st November 2014*	*NHS UK*
Reporting of Adverse Events in Clinical Trials	*15th September 2015*	*USZ Clinical Trials Center, Zurich*
Advanced User Vicon Nexus	*6th – 7th October 2015*	*Prophysics, Kloten*
Care of the Critically Ill Surgical Patient (CCrISP)	*14th – 16th October 2015*	*St James' University Hospital, Leeds, England*
Radiation Protection Course (Image Intensifiers)	*13th – 14th June 2016*	*Paul Scherrer Institute*
Approaches in Neurovascular Surgery	*24th June 2016*	*Addenbrooke's Hospital. Cambridge, England*
Basic Surgical Skills	*13th – 14th September 2016*	*Royal College of Surgeons, London, England*
Neuroanatomy of Operative Approaches	*15th – 16th September 2016*	*Leeds General Infirmary, Leeds, England*
SYNS Craniotomy Course	*28th – 29th October 2016*	*Anatomy Institute, Bern*

Publications

1. **Killeen T**, Easthope, CS, Filli L, Lőrincz L, Schrafl-Altermatt M, Brugger P, Linnebank M, Curt A, Zörner, B, Bolliger M. Increasing cognitive load attenuates right arm swing in healthy human walking. Royal Society Open Science 2017; 1: 160993

2. Filli L, Zörner B, Kapitza S, Reuter K, Lőrincz L, Weller D, Sutter T, **Killeen T**, Gruber P, Petersen J, Weller M, Linnebank M. Monitoring long-term efficacy of fampridine in gait-impaired patents with multiple sclerosis. Neurology 2017; 88: 1-10

3. **Killeen T**, Easthope CS, Filli L, Linnebank M, Curt A, Bolliger M, Zörner B. Modulating arm swing symmetry with cognitive load: a window on rhythmic spinal locomotor networks in humans? J Neurotrauma 2016 (Epub ahead of print), PMID: 27574966

4. Kockro RA, **Killeen T**, Ayyad A, Glaser M, Stadie A, Reisch R, Giese A, Schwandt E. Aneurysm surgery with pre-operative 3D planning in a virtual reality environment: Technique and outcome analysis. World Neurosurgery 2016; 96:489-99, PMID: 27609450

5. **Killeen T**, Rosner J, Jutzeler CR, Heilbronner R, Curt A. Spontaneous resolution of an extensive post-traumatic syrinx. Neurology 2016; 87:1299-1301, PMID: 27543642

6. Ryskeldiyev N, Olenbay G, Auezova R, **Killeen T**, Aldiyarova N, Akhmetzhanova Z, Cesnulis E, Akshulakov A. Brain tumor in an in-vitro fertilization-facilitated pregnancy: fourth ventricle anaplastic ependymoma in the second trimester. Journal of Neurological Surgery: Reports 2016; 77(2):86-88, PMCID: 4914713

7. Kockro RA, Amaxopoulou C, **Killeen T**, Wagner W, Reisch R, Stadie A. Stereoscopic neuroanatomy lectures using a three-dimensional virtual reality environment. Annals of Anatomy 2015, 201: 91-98, PMID: 26245861

8. **Killeen T**, Jucker D, Went P, Muthurajah V, Woon K, Cesnulis E, Czaplinski A. Solitary tumour-like mass lesions of the central nervous system: primary angiitis of the CNS and inflammatory pseudotumour. Clinical Neurology and Neurosurgery 2015; 135: 34-7, PMID: 26010394

9. Popugaev KA, Savin IA, Oshorov AV, Kurdomova NV, Ershova ON, Lubnin AU, Kadashev BA, Kalinin PL, Kutin MA, **Killeen T**, Cesnulis E, Melieste R. Postsurgical meningitis complicated by severe refractory intracranial hypertension with limited treatment options: the role of mild therapeutic hypothermia. Journal of Neurological Surgery: Reports 2014; 75(2): 224-9. PMID: 25485219

10. **Killeen T**, Wanke I, Mangiardi J, Cesnulis E. Ruptured, fusiform, distal lenticulostriate aneurysm causing intraventricular haemorrhage in a patient with antiphospholipid-negative Sneddon's syndrome. Clinical Neurology and Neurosurgery 2014; 116: 80-2. PMID: 24300743

11. **Killeen T**, Czaplinski A, Cesnulis E. Extradural spinal cavernous malformation: a rare but important mimic. British Journal of Neurosurgery 2014; 28(3): 340-6. PMID: 24073758

12. **Killeen T**, Tromop-van-Dalen C, Alexander H, Wickremesekera A. Bilateral retrocerebellar arachnoid cysts exerting mass effect and associated with cerebellar tonsillar ectopia in an otherwise healthy adult. Neurologia medico-chirurgica 2013; 53(4): 266-9. PMID: 23615422

13. **Killeen T**, Kamat A, Walsh D, Parker A, Aliashkevich A. Severe adhesive arachnoiditis resulting in progressive paraplegia following obstetric bupivicaine spinal anaesthesia: a case report and review. Anaesthesia 2012; 67: 1386-94. PMID: 23061983

14. **Killeen T**, Banerjee S, Dabbagh Z, Francis D, Warren S, Vijay V. Magnetic resonance pelvimetry as a predictor of operating time in laparoscopic resection of rectal cancer. Surgical Endoscopy 2010; 24(12): 2974-9. PMID: 20464426

15. **Killeen T**, Navalkissoor S, Buscombe J, Hall M. Voice recognition systems can cut nuclear medicine report turnaround time but may lead to more transcription errors [Abstract]. Nuclear Medicine Communications 2010; 31: 437-75, doi: 10.1097/MNM.0b013e328339ef84

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19. Baguley D, **Killeen T**, Wright J. International Health Links: an evaluation of partnerships between health care organizations in the UK and developing countries. Tropical Doctor 2006; 26: 149-54. PMID: 16884618

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21. **Killeen T** (ed.) International Health Links Conference: Summaries, reflections and feedback (2005). Available from the UK Department of Health website (accessed on 8th January, 2017).